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THE OPERATIVE TREATMENT OF DECUBITUS ULCER*

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SINCE the original report on the operative treatment of decubitus ulcer from this hospital,[1] considerable experience has been amassed, and a great impetus has occurred in this field in other Army hospitals. Most of the work has been done on paraplegic battle casualties.[2] The indications for the operative closure of decubitus ulcers in these patients no longer appear to be disputable. First and foremost, such a procedure effects, with little risk, a tremendous boost in the patient's morale and suddenly terminates the loss of tissue protein from the ulcer surface, thus favoring protein anabolism, increased appetite, strength, weight and general well-being.[3] It also removes the stigma of dependency on frequent dressings and allows an unhampered progress in ambulation.

General Considerations

The present report comprises the entire program of the management of decubitus ulcers in 130 paraplegic patients treated at Halloran General Hospital over a fifteen-month period, beginning in April, 1945. In this group were 62 patients with sacral ulcers, of which 42 were operated on at this hospital. Sliding, full-thickness flaps were employed in 38 cases, and split-thickness grafts in 4. The ulcers had been closed at other hospitals in 3 cases, by a rotating pedicle flap in 1 and by split-thickness grafts in 2. One of the last proved entirely unsatisfactory and was excised and replaced by sliding flaps. The ulcers in the remaining 17 cases were allowed to heal by secondary intention, either because they were small and superficial or because they were almost completely healed when the patients were transferred to us.

There were 49 cases of trochanteric ulcer. Of these, 31 were closed at this hospital by sliding, full-thickness skin flaps. Eight had been closed at other hospitals — 4 by sliding flaps, 1 by a rotated pedicle flap, and 3 by split-thickness grafts. Two of these cases proved rather unsatisfactory because of repeated ulcerations, and one has already been excised and replaced by sliding, full-thickness flaps.

There were 9 cases of ulcer of the ischial tuberosity. Only 4 of these patients were operated on.

There were a number of miscellaneous ulcers in the following order of frequency: over the calcaneus, dorsal spines, anterior superior iliac spines, fibular head, scapular spines, malleolus and patella. Only an occasional case was selected for operative closure — 2 over the dorsal spine, 1 over the anterior superior iliac spine, 1 over the scapular spine, 1 over the patella, and 1 of the anterior chest wall.

The objectives of the program were twofold: to obtain an early and complete closure and to obtain a closure that would be stable and satisfactory. Although the first objective could be readily realized by the application of split-thickness grafts to the denuded areas, it was soon observed that the end results thus obtained were often unsatisfactory. These grafts, which were intimately adherent to the underlying osseous prominence, with only a thin layer of fibrous tissue intervening, ulcerated repeatedly in response to the unavoidable trauma of the denervated skin. The grafts served as an expedient to obtain the first objective in patients who were not ready for the more extensive procedure, but the second objective was not considered to have been achieved, and these grafts were sometimes replaced by full-thickness flaps at a later date.

The preparation of a patient for the major procedure of closure with full-thickness skin flaps must receive careful consideration. The larger the ulcer, the more extensive the dissection of adjacent skin area to mobilize the skin and to close the defect without tension. Some degree of shock is unavoidable, even with transfusion, in the closure of large ulcers. Consequently, debilitated patients should not be subjected to such major procedures. Furthermore, the healing powers of such patients are poor, and they have less resistance to infection. The average paraplegic casualty was found to have lost about 50 pounds in weight the first month after injury. During this period of rapid and severe catabolism, when the protein stores of the liver and muscles were seriously depleted, most of the decubitus ulcers appeared — a great many of them within a few hours or a few days after injury. Although the appearance of the ulcers over bony

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prominences could in many cases be attributed to infrequent change of position and soiling during the rapid chain of evacuation from the front, in the last analysis it is likely that the skin is rendered more vulnerable to such traumas by the general catabolism, especially of proteins.[3]

Clinically, during this early phase, the appearance of the decubitus ulcer is characteristic. There is no evidence of healing process, but only of extending necrosis. The exudation of body fluids is profuse and thus, by a vicious circle, delays recovery. During this phase, treatment must be aimed at restoration of protein anabolism, forced oral feeding and parenteral alimentation with amino acids being used if necessary. Local infection must be controlled by conservative débridement of necrotic tissue and by systemic and local administration of chemotherapeutic agents. Anemia is controlled by repeated transfusions.

As soon as the local condition permits, as indicated by cessation of spreading necrosis, the appearance of healthy granulation tissue and the subsidence of active cellulitis, we believe that the ulcer should be closed by the temporary expedient of application of a split-thickness graft, since in most cases the patient is not prepared systemically for a major procedure. Many patients did not arrive at our hospital until several months had elapsed, and they had therefore passed successfully through the initial phase. Few of them, however, had been detained in the chain of evacuation long enough for skin grafts to be applied. The ulcers that most of them presented on admission were in the healing phase — that is, they were largely lined with a layer of granulation tissue, showed evidence of varying degrees of wound retraction and revealed only small areas of exposed nonviable or necrotizing fascia. Local acute inflammation had subsided, and exudation had materially decreased. The patients had already begun to regain weight and strength; they had passed the period of spinal shock, and automatic reflexes could be readily elicited. On admission, both aerobic and anaerobic cultures were taken routinely from ulcer surfaces. These cultures revealed a marked similarity to urinary and fecal flora, the following organisms being encoun-

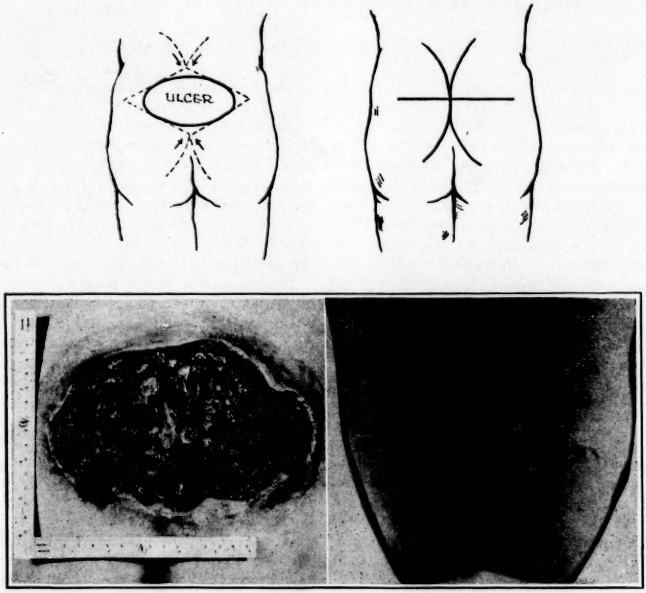

FIGURE 1. *Transversely Oval Sacral Decubitus (Case 1).*
The photographs show the appearances before and thirteen months after operation.

tered: *Proteus vulgaris*, *Escherichia coli*, *Aerobacter aerogenes*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, streptococcus and finally some of the Clostridia, usually of low pathogenicity. Other anaerobes were rarely found. On the basis of experience bacteriologic findings were, in general, disregarded although an attempt was made to protect the patient from invasive organisms by local dusting of the operative surface with plasma-penicillin powder and by the administration of penicillin for five days preoperatively and, when indicated by the presence of *Staph. aureus* or streptococcus, for several days after operation. In the selection of patients for the major operative procedure, more reliance was placed on the clinical appearance of the ulcer. An ulcer was considered ready for operation when it became free from all evidence of recent cellulitis, when it presented a healthy granulating surface, when all non-viable tissue had separated, when exudation had practically ceased and when the wound margins began to show evidence of retraction from healing and finally showed invasion by a gray-white peripheral zone of proliferating epithelium.

Most patients required no anesthesia at the time of operation, since the ulcer occurred well below the sensory level. When anesthesia was required, endotracheal administration of ether was used almost exclusively, since it was considered safest with the patient in the prone position. Continuous spinal anesthesia was rarely employed. When only the proximal part of the operative field was sometimes infiltrated with procaine. The general operative technic has been described in a previous paper,[1] but the following technical details should be reemphasized: sharp dissection, excision of all scarred tissue, fine-silk hemostasis, the development of flaps sufficiently extensive to allow closure without tension, thorough irrigation of the operative-wound surface with physiologic saline solution before closure, followed by dusting with plasma-penicillin

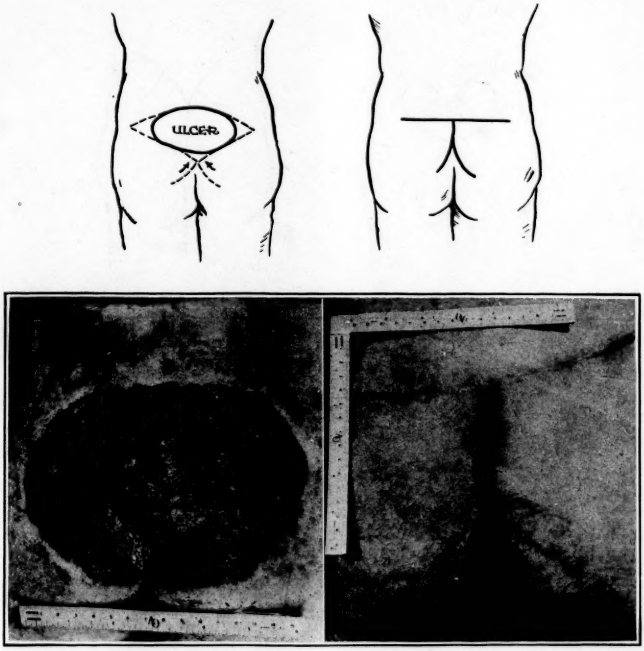

FIGURE 2. *Transversely Oval Sacral Decubitus (Case 2).*
The photographs show the appearances before and five weeks after operation.

powder, and the maintenance of a pressure dressing for several days postoperatively.

Sacral Decubitus Ulcers

The sacral region was the most frequent site of decubitus ulceration. Sixty-two of the 130 patients presented sacral ulcers, and 42 of these were selected for operation. Of these, the ulcers in 38 were closed by sliding, full-thickness flaps; split-thickness grafts were employed in 4 cases either because the ulcer was too large (in 1 case, measuring 30 by 24 cm., butterfly in shape and extending well over the posterior superior spines above and the ischial tuberosity below) or because the patients were too ill (2 cases) or so spastic in flexion that they could not be placed in the prone position (in 1 case reoperation was subsequently performed, and the ulcer closed by full-thickness flaps).

Of the 38 cases selected for closure by full-thickness flaps, the ulcers were large in 37, measuring more than 6 cm. in diameter, and small in 1. Sacral ulcers were found to vary somewhat in shape, depending to some extent on the local conformation of the skeleton. The usual type was transversely oval, having a slightly greater transverse than vertical diameter (Fig. 1). There were 27 cases of this type, in which closure was effected by excision of the ulcer in a transversely flattened diamond pattern. Curvilinear incisions were then made from the superior angle upward and outward into each lumbar region, and similar incisions from the inferior angle downward and outward into each buttock. The four sector flaps thus outlined were then raised from the fascial investment of the gluteal muscles, and each was rotated centrapetally to approximate its fellow of the same side transversely and of the other side vertically, thus closing the defect. The average size of the ulcers was 14 cm. in the transverse diameter and 10 cm. in the vertical. The largest measured 24 by 12 cm. and healed by first intention.

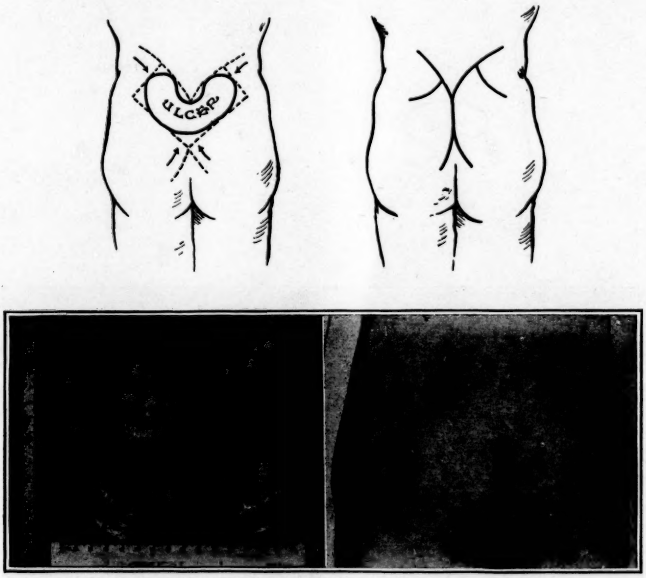

Figure 3. *Shield-Shaped Sacral Decubitus (Case 3).*
The photographs show the appearances before and fourteen months after operation.

Some of the smaller ulcers of this type were closed simply by the sliding of two flaps from the buttocks below after excision of the ulcer in the pattern of a triangle with the apex pointing caudally at the coccyx (Fig. 2).

Four of the largest sacral ulcers, which were classified as shield shaped because there were horn-

like extensions over the posterior superior spines, were closed by a modification of the first method, the upper sector flap being smaller than the lower (Fig. 3).

There were 6 vertically oval ulcers, which were closed by elliptical vertical excision, with triangular extensions into each buttock (Fig. 4).

Of the small sacral ulcers, only one was closed by rotation of a single flap upward from one buttock (Fig. 5). Although this method has been mentioned by other authors, it is not considered suited to the closing of large sacral ulcers.

There were few serious complications. Only 1 patient developed a postoperative skin necrosis, resulting in a loss of an area 2 by 4 cm., which was surgically excised and successfully skin grafted. There were 2 cases of extensive wound disruption, but both healed by first intention on resuture. There were small dehiscences at the confluence of the four flaps in 5 cases, but these were all 2 cm. or less in diameter and healed uneventfully in a few weeks. There was only one frank wound infection, and this significantly occurred in the only case in which absorbable gauze was used for hemostatic purposes. The infection subsided promptly on removal of the foreign body. We do not desire to condemn the use of this gauze, but merely to caution against its use immediately underlying a suture line, particularly where there is a subcutaneous bony prominence. Sacral cases sometimes presented accumulations of sterile serous fluid that were treated by repeated aspirations. Drains were not used at any time in the entire series. One case developed a large hematoma underlying the flaps, and this was evacuated surgically.

Many of the sacral operations were performed more than a year ago. There have been few late complications. One patient developed an ischemic

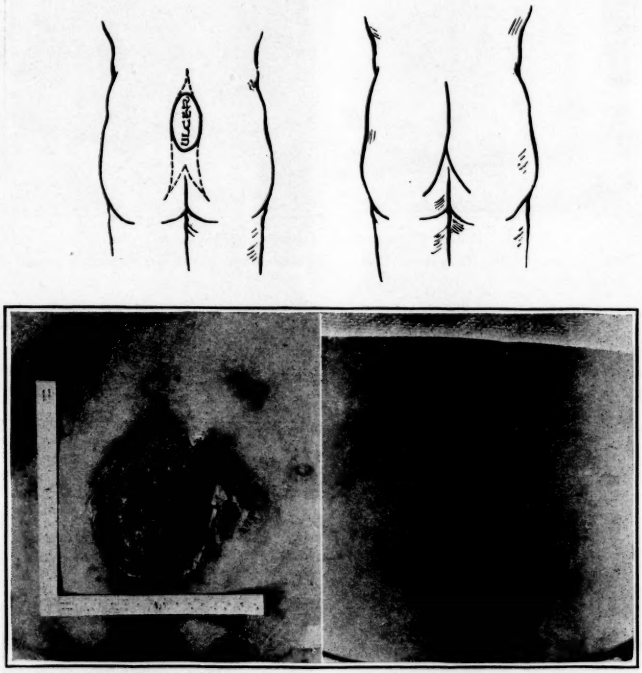

FIGURE 4. *Vertically Oval Sacral Decubitus (Case 4).*
The photographs show the appearances before and fourteen months after operation.

necrosis of a portion of a postoperative flap three weeks after operation, owing to sitting in a wheel chair for six hours without a change of position. Another developed a secondary ulcer six months postoperatively, following immobilization for three days because of serious illness. The ulcers in both cases were closed by further advancing of the same flaps. These cases merely illustrate that the skin must receive the same care postoperatively as the unbroken skin.

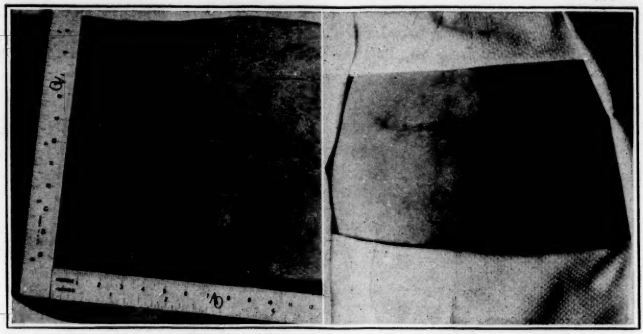

FIGURE 5. *Small Sacral Decubitus (Case 5).*
The photographs show the appearances before and eleven weeks after closure by rotating a single flap from the buttock.

TROCHANTERIC ULCERS

From the beginning of the program, it was recognized that the successful closure of a trochanteric ulcer would be a much more difficult accomplishment. An analysis of the situation discloses the nature of these difficulties. Thus, the skin is usually drawn tightly over the hip, so that more extensive dissection is required to cover relatively small defects. It is difficult to immobilize the hip without placing the patient in a plaster spica. Any motion of the hip — especially flexion and adduction, which are frequent in reflex spasms — tends to disrupt the repair of soft tissues over the trochanteric prominence. The superficial appearance of the ulcer generally belies its true extent, since there is usually considerable skin retraction about the ulcer and an extensive subcutaneous defect where the trochanter

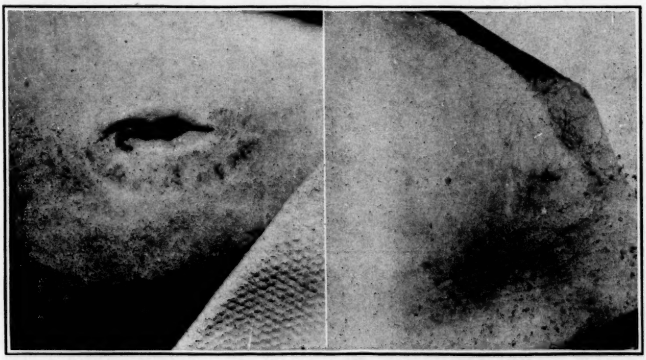

FIGURE 6. *Small Trochanteric Decubitus (Case 6).*
The photographs show the appearances before and three months after linear closure.

has worn away the fascia lata to produce a so-called "false bursa."

A total of 49 cases of trochanteric ulcer have been observed in 43 patients. Thirty-one of these were operated on at this hospital. In 4 cases the ulcer had been closed before admission to this hospital. One of these had been closed by a rotating full-thickness flap, the donor site being covered by a split-thickness graft; this procedure proved quite satisfactory. The ulcers in 3 other cases had been closed merely by the application of split-thickness grafts, which proved rather unsatisfactory. One was finally excised and covered by a full-thickness flap.

In general, the operative methods we employed fell into three groups.

Linear closure. Trochanteric ulcers are usually vertically oval. For those less than 3 cm. in the transverse diameter, elliptical excision of all scar tissue along with the granulation tissue base and subsection, to raise a substantial anterior and posterior flap, usually allowed the approximation of these flaps without undue tension (Fig. 6).

Single sliding flap. Trochanteric decubiti over 3 cm. but less than 6 cm. in the transverse diameter could usually be closed by the sliding of a semicircular flap from the corresponding buttock. The incision was usually continued from the inferior angle of the ulcer medially and posteriorly along the inferior gluteal fold. A single large flap was developed and rotated laterally to cover the defect (Fig. 7).

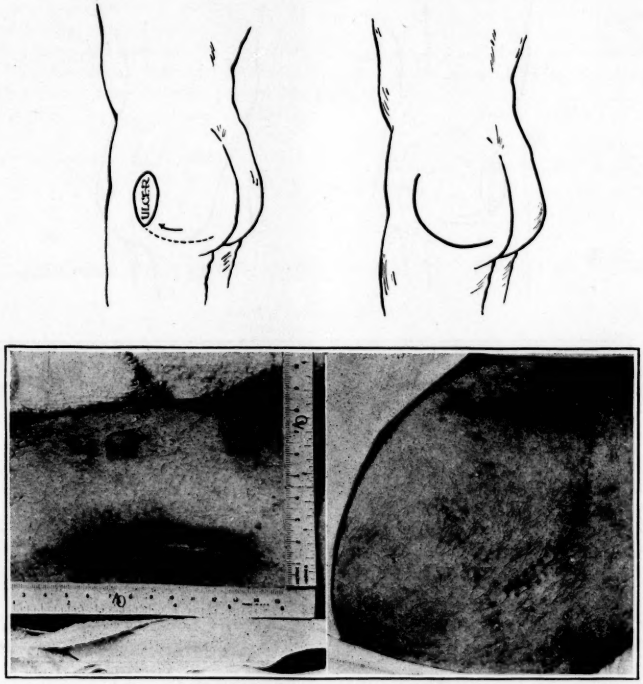

FIGURE 7. *Trochanteric Decubitus (Case 7).*
The photographs show the appearances before and four months after closure by the single-flap method.

Double sliding flaps. Trochanteric ulcers over 6 cm. in the transverse were closed by the development of an additional semicircular flap anteriorly and superiorly from the anterior surface of the thigh, thus creating an S-shaped wound on approximation (Fig. 8).

In this series 5 patients were treated by linear closure, 20 by single sliding flaps, and 6 by double sliding flaps. In general the results were not so good as those in the management of sacral ulcers. Of the ulcers with linear closures, 3 healed by first intention, and 2 developed small dehiscences. Of the 21 single-flap closures, 13 healed by first intention, and 4 developed partial dehiscences. Three of the latter patients were severely spastic, and another was undernourished and failed to heal any of his operative wounds. It is believed that postoperative immobilization in a padded plaster spica, with the hip abducted, will improve the results in this type of surgery.

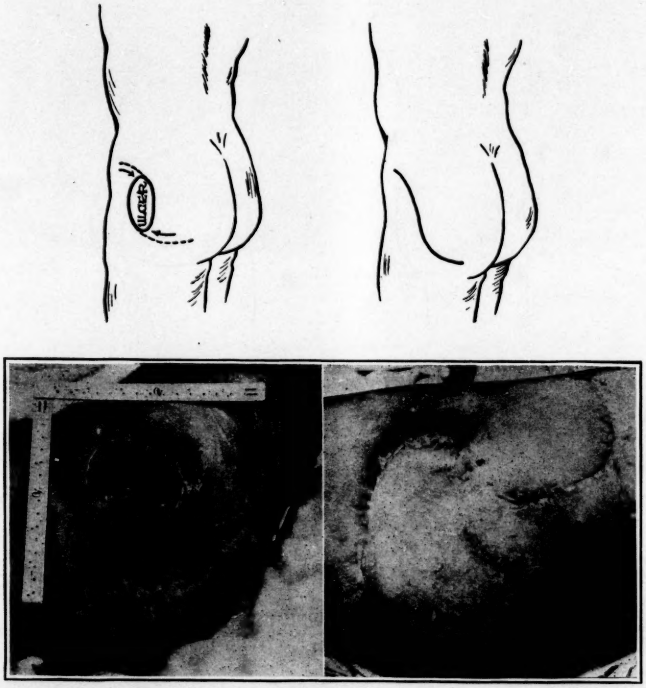

FIGURE 8. *Trochanteric Decubitus (Case 8).*
The photographs show the appearances before and two months after closure by the double-flap method.

ISCHIAL DECUBITUS

As the program of rehabilitation of paraplegic patients progressed and more of them left their beds for the wheel chairs, various lesions of the ischial regions were encountered with greater frequency. Most paraplegic patients have atrophic gluteal muscles, as a result of which they present a great deal of loose skin for the closure of sacral ulcers, but little padding for the ischial tuberosity. Clinically, these patients sometimes developed redness and swelling in the ischial regions. At first these lesions were often mistaken for early ischial abscesses, but it was soon discovered that incision led to the formation of sinuses communicating with chronically infected ischial bursas, curable only by excision of the bursa. Preferably, the early treatment consists of cessation of weight bearing and systemic chemotherapy. The signs of inflammation usually subsided slowly with this regime. Once the superficial tissues have ulcerated over the ischial tuberosity, however, the ulcer is best treated surgically by excision and linear closure. So important is complete immobilization in the postoperative treat-

ment of these lesions, that we have come to rely on nothing short of the well padded plaster spica. Of the 4 patients operated on, 2 with ulcers that healed by first intention were thus treated.

Miscellaneous Types

A relatively frequent decubitus that continues to challenge the surgical program is that over the calcaneus. From our own experience and that of others, it was concluded that split-thickness grafts would be undesirable. Local closure with full-thickness sliding flaps was also not feasible, and pedicle flaps from the thighs were considered impractical. The patients were therefore treated by nonoperative methods and not allowed to delay ambulation.

In the closure of dorsal ulcers, it seems advisable to resect the protruding spinous process before closure.

Summary and Conclusions

The treatment of large decubitus ulcers in a young paraplegic patient is a surgical problem.

The more frequent varieties of decubitus ulcer — sacral, trochanteric and ischial — may be closed by sliding full-thickness skin flaps. Surgical experiences in performing such closures on a large number and variety of ulcers are reported. The important details of these procedures are presented.

Full-thickness skin closure of decubitus ulcers gives a much more satisfactory result than either secondary healing or closure with split-thickness graft. The procedure is sometimes a relatively formidable one, and is not recommended for the closure of decubitus ulcers in the aged and debilitated.

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WOUND INFECTIONS WITH FRIEDLÄNDER BACILLUS FOLLOWED BY MENINGITIS

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THE Friedländer bacillus (*Klebsiella pneumoniae*), under the right conditions, is highly virulent for man. Hence, although infections with this organism are not frequent, they deserve consideration out of proportion to their incidence. Appreciation of this fact is essential so that cases may be recognized and treated early with methods now in use and also in order that new and more effective remedies may be developed. With this in mind, 3 cases of wound infection with Friedländer bacillus, followed by fatal meningitis, are presented below.

There are surprisingly few reports in the literature containing careful bacteriologic studies of wound infections and only a few bare references to the role of the Friedländer bacillus. Riggenbach[1] was perhaps the first to report a case of wound infection due to the organism. Levaditi,[2] reporting on wound infections in World War I, mentioned that the organisms most generally found were staphylococci (in 85 per cent of cases), Friedländer bacillus, *Clostridium welchii*, streptococci, the coli group and *Pseudomonas aeruginosa*. Pulaski, Meleney and Spaeth[3] found that staphylococci could be recovered from nearly every wound. Streptococci were isolated from half the wounds. Gram-negative organisms, such as *Escherichia coli*, *Proteus vulgaris*, *Eberthella typhosa*, *Ps. aeruginosa* and *K. pneumoniae*, were found in a fourth of the cases. Among the numerous other reports on wound infections there is to my knowledge no mention of the Friedländer bacillus. The First General Medical Laboratory, which received a fair sampling of cultures from United States Army hospitals in the United Kingdom, informed me in October, 1944, that within several weeks they had identified the bacillus in wound cultures in 6 cases. It is my impression that if careful cultures of wounds were done routinely, the bacillus would be found quite frequently. Its seeming rarity in wound infections may also be explained in part by the tendency to pass off all gram-negative rods found in wound cultures as coliform organisms.

Meningitis due to Friedländer bacillus is apparently rare. In 1938 3 cases secondary to pneumonia were reported.[4] Ransmeier,[5] in 1943, reported 1 case and referred to 29 others in the literature. In approximately half the cases the meningitis followed infections of the middle ear or sinuses. In the remainder it followed pneumonia, cholecystitis or colitis with bacteremia. None of the cases were related to trauma. Hence the finding of 3 cases of meningitis due to Friedländer bacillus following war wounds seems worthy of reporting.

Bacteriology

The organism is a gram-negative rod, 0.5 to 5 microns in length and approximately half as wide.

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Consequently, it may be either quite long or coccoid in shape. It may be seen singly or in short chains. It is nonmotile, nonspore forming, aerobic and facultative anaerobic. It has a distinct, thick capsule, which is seen on direct smears from infections with the organism. The organism grows readily in the usual laboratory mediums. On solid mediums the colonies are large and opaque and have a slimy, mucoid appearance.

Julianelle[6] identified several distinct types by means of agglutination and animal protection tests. These are groups A, B and C, as well as a heterogeneous group known as "X." The distinction between the different types depends on chemical differences in the polysaccharide of the capsule. The organism has a rather wide distribution, being found in the soil, air and water. It also occurs as a saprophyte in the upper respiratory and intestinal tracts in a small percentage of normal human beings.

Infections due to the bacillus may be conveniently divided into pulmonary and extrapulmonary groups.

Pulmonary Infections

Approximately 1 to 3 per cent of all pneumonias are due to *K. pneumoniae*. This form of pneumonia is most virulent, but many cases run a course with a temperature below 101°F.[4] The pneumonia is lobar in character, but involvement of several lobes is frequent. The sputum, in the majority of cases, is a characteristic homogeneous emulsion of blood and mucus — brick red in color and unlike the prune juice sputum of pneumococcal pneumonia or the bloody sputum often found with tuberculosis. A direct smear shows many large, gram-negative encapsulated bacilli. The organism can be recovered in pure culture by mouse inoculation or by culture of the sputum on blood-agar plates. Bacteremia occurs in the majority of cases but is ordinarily not intense. The most frequent complications are abscess formation and empyema; meningitis and purulent pericarditis occur more rarely. The mortality in untreated cases is over 90 per cent.

Chronic lung infections due to this organism are less frequent and are often misdiagnosed.[7] Nonputrid lung abscesses are frequent, and these are usually located in one or both upper lobes. Hence, the disease is often mistaken for pulmonary tuberculosis unless the case is critically evaluated. It is by no means easy to find the organism in the chronic stages, since secondary invaders may overgrow it.

Extrapulmonary Infections

These have been described in detail by Baehr, Schwartzman and Greenspan[8] and more recently by Jaffe.[9] Intra-abdominal infections are usually secondary to perforative lesions of the large intestine, such as appendicitis, diverticulitis and carcinoma. Abscess formation or generalized peritonitis may occur. Secondarily, subphrenic or liver abscess and, occasionally, septicemia may result. Biliary-tract infections, which are next in frequency, usually occur in association with gallstones. Purulent otitis media and mastoiditis are not rare and may lead to cavernous sinus thrombosis or meningitis.

It is of interest that extrapulmonary infections in general have a relatively low mortality (17 to 30 per cent). The mortality in cases complicated by bacteremia is about 75 per cent, and that with meningitis is over 90 per cent.

Treatment

Specific horse antiserum has been used with varying results. Bullowa, Chess and Friedman[10] reported a reduction of mortality in pneumonia due to Friedländer bacillus, but my own experience with serum was disappointing.[4]

In recent years the sulfonamides have been used with some success. I[7] first employed sulfapyridine in 1938 in the treatment of 4 cases. The patients survived, although they developed the chronic form of the disease. More recently, Feinstone and his co-workers[11] showed that in experimental infections in mice, sulfadiazine is superior to other sulfonamides, and clinical reports have described the same results. Appelbaum[12] noted recovery in a fair percentage of cases of meningitis treated with sulfonamides and, more recently, in a case treated with streptomycin. Penicillin has not been found effective.[13, 14] In Cases 1 and 2 reported below, the organism was resistant in vitro to concentration of penicillin as high as 1000 units per cubic centimeter — levels that are impossible to attain in the blood stream. More hopeful, however, is recent experimental work by Heilman,[15] which indicates that streptomycin may have definite value.

Case Reports

Case 1. A 26-year-old soldier was wounded in France on August 8, 1944, by mortar-shell fragments, sustaining penetrating wounds of the left buttock and a fracture of the left ilium. He received treatment in a field hospital and was evacuated to England on August 20.

The wound of the left buttock showed a mucopurulent discharge, and treatment with sulfadiazine was instituted (1 gm. every 4 hours). On August 24 the temperature rose to 104°F., the neck was stiff, and Kernig's sign was positive. Cultures from the wound and blood were positive for Type A *K. pneumoniae*. A spinal tap yielded a cloudy fluid containing 5200 polymorphonuclear cells per cubic millimeter; the sulfadiazine level was 3.8 mg. per 100 cc. A direct smear of the sediment showed many gram-negative, encapsulated bacilli. Examination of the blood showed a white-cell count of 14,800, with 82 per cent segmented neutrophils, 8 per cent young forms and 10 per cent lymphocytes.

Treatment with penicillin was started at 4 p.m., the patient receiving 30,000 units intravenously, followed by 30,000 units intramuscularly every 4 hours. At 6 p.m. 5000 units of penicillin was given intrathecally, followed by 5 gm. of sodium sulfadiazine intravenously. The temperature rose to 107°F. at 10 p.m. Analysis of the spinal fluid showed essentially the same findings, except that the sulfadiazine level was 9.3 mg. per 100 cc.; 5000 units of penicillin was instilled intrathecally. The patient did not respond to therapy and died at 9 o'clock on the following morning.

Autopsy. Post-mortem examination disclosed greenish-yellow pus covering the entire brain and spinal cord. The choroid plexus contained a number of small collections of pus. Careful examination of the spinal cord revealed no tear of the meninges.

Dissection of the wound of the left hip demonstrated a severe destructive process involving the deep muscles. The internal and middle ears appeared normal. Cultures from the meninges, the blood and the wound showed a pure growth of *K. pneumoniae.*

CASE 2. A 19-year-old soldier was wounded by shell fragments on August 13, 1944, sustaining a scalp wound and fracture of the skull. He did well and was evacuated to England on September 6. The general condition was good, but the wound exuded some serous material. Roentgenograms of the skull showed several indriven bone fragments near the falx and a metallic foreign body at the base of the skull.

Operation was done for depressed skull fracture on September 9, devitalized brain and free bone fragments being removed. Two days later the patient developed signs of meningitis. A spinal tap yielded a purulent fluid that contained Friedländer bacilli in pure culture. The patient was treated intensively with sulfadiazine and penicillin intramuscularly and intrathecally, but showed no response, death occurring on September 13.

Autopsy. Post-mortem examination showed the brain to be covered by a massive exudate of fibrin and pus that contained many encapsulated bacilli. A brain abscess was seen in the hypothalamus, in the center of which a metallic foreign body was found.

Most of the left lung was consolidated in the stage of red hepatization. Culture of the wound, the abscess, the meninges, the left lung and the blood showed *K. pneumoniae.* It is of interest that the abscess had remained quiescent for 4 weeks before it ruptured, leading to septicemia and meningitis.

CASE 3. A 29-year-old soldier was wounded by shell fragments on September 9, 1944, sustaining penetrating wounds of the abdomen, with perforation of the jejunum and descending colon. He also suffered a deep laceration over the sacrum, with fractures of the left transverse processes of the 3rd, 4th and 5th lumbar vertebras. This was followed by left-foot drop. The jejunal perforations were sutured, and a colostomy was done at a field hospital. The patient received a blood transfusion, 20,000 units of penicillin and some sulfadiazine (quantity not stated) and was evacuated to England on September 28.

The temperature ranged from 99 to 102°F. He became restless and irrational. On October 1, a spinal tap yielded a milky fluid containing 90,000 polymorphonuclears per cubic millimeter. Gram-negative encapsulated bacilli were seen in the smear, and culture showed *K. pneumoniae.* Death occurred on the same day.

*Autopsy.** Post-mortem examination revealed the laceration over the sacrum to extend into a large abscess 12 cm. in diameter. The dura and several fibers of the cauda equina on the left were lacerated, and beneath the pia, a green, purulent exudate was noted. A similar exudate was found over the cortex and base of the brain. The sinuses and middle ear were normal.

A small amount of green pus was expressed from around the apparently clean colostomy. The lungs showed several infarctions in both lower lobes and an embolus in one of the branches of the left pulmonary artery.

Culture of the heart's blood was negative; culture from the brain, from the area about the colostomy and from the laceration in the sacral region showed *K. pneumoniae.*

The laceration of the sacral region involving the dura and cauda equina was apparently the site of an unrecognized Friedländer bacillus infection that had gained entry into the subarachnoid space, resulting in meningitis.

DISCUSSION

The patients in the cases presented above sustained shell-fragment wounds complicated by meningitis, but the pathogenesis of the meningitis was different in each case. In Case 1 the wound infection was followed by bacteremia and meningitis. In Case 2 there was a brain abscess around a shell fragment. The abscess ruptured, resulting in meningitis and septicemia with death on the thirty-first day. The patient in Case 3 sustained lacerations of the sacral region and of the spinal dura. The wound was the site of *K. pneumoniae* infection that had extended directly through the torn dura leading to meningitis and death twenty-two days after injury. The organisms in Cases 2 and 3 were not typed, but their virulence and the finding of positive cultures in the blood and the meninges are presumptive evidence that they were Friedländer bacilli and not mucoid coliform organisms.

The origin of the Friedländer bacillus is in doubt. It is possible that the shell fragments carried the organisms into the tissues, but it is likelier that, in at least 2 of the cases, infection occurred during the period of hospitalization. This may have been due to fecal contamination, but since the organism is a frequent inhabitant of the upper respiratory tract it seems probable that the wounds became infected when dressings were changed. The wearing of masks by attending personnel and the strict observance of operating-room technic during routine dressings of wounds are often not practiced.

There were no features in the appearance of the wounds or in the clinical course that distinguish these cases from other wound infections. Such a differentiation could be attained only by routine bacteriologic study of infected wounds. Cultures were not made until an unusual complication had occurred. This was unfortunate because for some reason in each case a long latent period between the time of injury and the development of meningitis would have provided more time for treatment had the diagnosis of infection with Friedländer bacilli been made earlier.

The patient in Case 1 received adequate sulfadiazine therapy, but this did not prevent the development of bacteremia and meningitis. The addition of penicillin to the treatment after these complications had ensued had no effect. The second case was not diagnosed until forty-eight hours before death. Intensive therapy with penicillin and sulfadiazine had no effect. The patient in Case 3 was not given therapy for the infection.

SUMMARY

Three fatal cases of wound infection with Friedländer bacillus followed by meningitis are reported. Meningitis in one case was secondary to bacteremia; in another, it was due to direct extension through the torn dura of the spinal cord, and in the third it followed rupture of a brain abscess surrounding a metallic fragment.

The origin of the wound infections is in doubt, although it seems likely that they represented cases of hospital infection, and the most important factor in hospital infection of wounds appears to be droplets from the nose and throat. Hence, the need for the

*Performed by Lieutenant-Colonel Jerome I. Silverman, chief of the laboratory of the One Hundred and Twenty-Third General Hospital, to whom I am indebted for permission to publish this case.

wearing of masks by attending personnel and for the observance of strict operating room technic when wounds are dressed should be emphasized.

Routine culture of wounds should be made as soon as infections are apparent. In this way the physician will have precise bacteriologic data and will be able to start treatment at once. Treatment with sulfadiazine and penicillin was unsuccessful in 2 cases. It would be rash to draw any conclusions from this, but on the basis of past experience and of reports in the literature, sulfadiazine appears to be the most effective agent in use at present. Newer antibiotics, such as streptomycin, give promise of greater effectiveness and should be given further experimental and clinical trial. In infections with such a virulent organism, however, no remedy will prove generally effective unless bacteriologic diagnosis is made early.

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ADDISON'S DISEASE ASSOCIATED WITH AMYLOIDOSIS FOLLOWING THERMAL BURNS*

Report of a Case

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BOSTON

ADDISON'S disease associated with amyloidosis of the adrenal glands is uncommon, less than 20 cases having been reported. Amyloidosis of the adrenal glands accounted for about 2 per cent of the cases of Addison's disease reported by Guttman.[1] Amyloidosis following thermal burns has rarely been reported,[2] and Addison's disease associated with amyloidosis following burns has not been reported to our knowledge. The following case presented such a combination.

A 42-year-old Negress with a noncontributory past history was admitted to the hospital May 10, 1944, with flame burns involving 15 per cent of the body surface, chiefly deep, and severe thermal respiratory-tract injury. Eighteen hours after admission a tracheotomy was performed because of marked stridor and air hunger. There were no further respiratory difficulties, the tracheal tube being removed on the 10th day.

The surface burns were dressed initially with dry, sterile, pressure dressings without anesthesia or preliminary cleansing. Subsequent dressings were, for the most part, also dry-pressure dressings.

During the first 6 weeks the temperature varied between 100 and 102°F. Sulfadiazine, in doses of 6 gm. a day, had been started on entry and was continued for 1 week. Following this 15,000 units of penicillin was given intramuscularly every 3 hours for 6 weeks. There were no toxic reactions to either drug.

Intravenous infusions of Amigen* were started on the day after entry and during the first 2 weeks constituted the chief protein nutriment, 3000 cc. being given daily. During that time the patient appeared to be in apparent positive nitrogen balance and to be maintaining her weight. The plasma protein concentration, however, fell from 7.2 gm. per 100 cc. of plasma on entry to 6.3 gm., and the albumin from 4.2 to 2.8 gm. Oral administration of 225 mg. of ascorbic acid, 9 mg. of thiamine chloride, 6 mg. of riboflavin, 60 mg. of nicotinamide, 15,000 units of vitamin A and 3000 units of vitamin D was given daily, as well as 1.5 cc. of crude liver extract (Wilson) intramuscularly.

During the 3rd week the intravenous infusions of Amigen were omitted, and the patient went into negative nitrogen balance, the intake having fallen to 6 gm. of nitrogen and 1600 calories daily. The vitamin intake remained the same. The plasma protein concentration, however, remained unchanged. By the 5th week, with urging and special nursing care, the intake was gradually raised to 40 gm. of nitrogen and 3500 calories daily, with dried beef serum as an oral supplement to the diet. The patient again appeared to be in

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positive nitrogen balance. The beef serum supplement was continued for 8 weeks. The vitamin intake was unchanged.

The hemoglobin, which had been normal on admission, fell to 55 per cent by the 5th day and remained between 55 and 60 per cent until the 7th week. Thereafter, sufficient type-specific whole-blood transfusions were given to maintain the hemoglobin between 80 and 95 per cent. In the 7th week skin grafting of part of the burned area by the Padgett dermatome technic was done for the first time and was repeated in the 8th and 11th weeks. The takes of the graft were good, but the donor sites failed to epithelialize in the next 5 weeks. During this period the food intake declined, and the patient lost weight and strength. The vitamin supplements were not changed. The temperature varied between 98 and 100°F.

In the 5th and 6th months, under a regime of special nursing care and forced feedings, consisting chiefly of milk with added milk powder, sugar and Amigen, the patient's condition improved markedly. The vitamin intake remained the same. She gained weight and strength and was getting out of bed. The plasma protein and albumin concentrations, which had fallen to 5.4 and 2.4 gm. per 100 cc., respectively, at the 8th week rose to 7.5 and 3.1 gm., respectively. The temperature was normal, and the donor sites had almost completely epithelialized.

From the seventh month on, it was not possible to keep the patient on special nursing care. The food intake and general condition gradually deteriorated. In the 7th and 8th months 15,000 units of vitamin A, 3000 units of vitamin D, 725 mg. of ascorbic acid, 9 mg. of thiamin, 6 mg. of riboflavin, and 1.5 cc. of crude liver extract (Wilson) were given daily. In the 9th month through the 12th month the patient received in addition 2 cc. of halibut-liver oil with viosterol (Parke–Davis). Thereafter, the fat-soluble vitamin supplements were omitted, and she was given 500 mg. of ascorbic acid, 15 mg. of thiamin, 20 mg. of riboflavin, and 150 mg. of nicotinamide daily. Loss of strength and weight were marked. The donor sites and some of the grafted areas broke down. The granulations became exuberant and friable. The fever was low grade. Cultures of the wounds throughout the course showed hemolytic *Staphylococcus aureus* as the predominant organism, with alpha-hemolytic and beta-hemolytic streptococcus, diphtheroids and *Proteus vulgaris* also present in the majority of cultures.

In general, the white-cell counts were elevated, the majority being about 15,000, with occasional extremes of 8000 and 30,000. The icteric index throughout was 4. Cephalin-flocculation, hippuric acid, bromsulfalein and Quick prothrombin determinations were made on several occasions during the first 7 months, and were always within normal limits.

Intravenous glucose-tolerance tests demonstrated a significantly elevated blood glucose concentration 2 hours after the injection of 25 gm. of glucose on the day of entry, but a normal level on the 8th day. Intravenous insulin-tolerance tests were done on the 1st, 9th and 56th days. On the 1st day the level 2 hours after the injection of the insulin was significantly low, the fasting level being 98 mg. and the 2-hour level 24 mg. per 100 cc. On the 9th and 56th days, reactions were normal.

The urine, which since entry had shown albumin and white cells, began to show large numbers of red cells in the sediment on occasional days during the 11th month. No casts were seen. The specific gravity of the urine became fixed at the end of the 12th month at 1.010. Urea clearance and phenolsulfonphthalein excretions were low. The non-protein nitrogen concentration in the plasma, which had been normal on entry and for the next 11 months, rose to 49 mg. per 100 cc. in the 12th month (Table 1), and then rose slowly, reaching a level of 75 mg. per 100 cc. by the end of the 12th month. The urine was negative for tubercle bacilli by the guinea-pig technic, and a catheterized specimen was negative for other bacteria.

The blood pressure, which had been about 120/80 on entry, dropped to 105/70 by the 9th month and to 90/60 by the 12th month. The weight at that time was 90 pounds, as compared with an estimated weight of 125 pounds on entry. The granulations were still friable, and grafting could not be done. The patient was weak but alert. In the 13th month she became irrational and stuporous for a period of 6 hours following the administration of 0.1 gm. (1½ gr.) of Nembutal. She had previously received this dose of Nembutal on many occasions without any untoward reaction. On the next day a dressing was done under cyclopropane anesthesia without preliminary medication. Following this she became delirious. The blood pressure fell to 85/40. On the following day she had an epileptiform seizure and became comatose. The blood pressure had fallen to 70/40, and the pulse was rapid and thready; the extremities were cold and clammy, and the temperature 97°F. by rectum. The plasma nonprotein nitrogen had risen to 118 mg. per 100 cc.; the chloride and the sodium, which had been normal, had fallen to 68 and 128 milliequiv. per liter, respectively. The carbon dioxide combining power on the next day was 13 millimols per liter — it had been normal on entry. Pertinent laboratory data during the hospital course are presented in Table 1.

The diagnosis of Addison's disease in crisis was made by one of us (H. T.), and therapeutic measures were accordingly taken. Plasma and glucose in isotonic saline solution were given intravenously in the next hour. This produced a slight rise in the blood pressure to a level of 90/50 and a lowering of the pulse rate to 88. Immediately thereafter a regime of adrenocortical extract, desoxycorticosterone, testosterone propionate and additional intravenous saline solution and glucose was begun.

During the 1st day 50 cc. of adrenocortical extract, 35 mg. of desoxycorticosterone and 50 mg. of testosterone were given, and 25 gm. of sodium chloride and 300 gm. of glucose were administered intravenously in the form of 10 per cent glucose in isotonic saline solution. Within 12 hours, the patient had regained consciousness and had no further epileptiform

TABLE 1. *Pertinent Laboratory Data.*

Hospital Day	Nonprotein Nitrogen	Total Protein	Chloride	Sodium	Carbon Dioxide Combining Power	Blood Pressure
	mg./100 cc.	*gm./100 cc.*	*milliequiv./liter*	*milliequiv./liter*	*millimols/liter*	
1	28	7.1	99	144	25	120/80
358	49	6.4	—	—	—	50/60
366	62	6.7	—	—	—	115/80
370	75	6.5	—	—	—	100/60
380*	118	—	68	128	—	70/40
381	98	—	84	—	13	110/50
385	87	5.1	80	135	16	—
386	78	5.5	—	—	—	95/55
390	118	—	69	—	20	100/65
391	80	—	100	—	—	95/55
393	67	5.0	69	—	25	100/65
395	78	5.0	75	—	26	82/50
397	60	5.0	100	136	22	104/50
401†	78	5.1	100	—	—	96/60
414‡	116	4.8	—	—	—	85/45
415	143	5.8	87	130	13	70/30

*Diagnosis of Addison's disease, in crisis, made at this time, and adrenocortical extract, desoxycorticosterone, testosterone and sodium chloride therapy begun.

†Hormonal treatment discontinued.

‡Hormonal treatment resumed.

seizures. The blood pressure had risen by the following day to 110/50, and she was talking coherently. The rectal temperature had risen to 99°F. The blood sugar was normal. On the 2nd day 5 mg. of desoxycorticosterone and 30 cc. of adrenocortical extract in divided doses were given. The sodium and glucose intakes were about the same as on the previous day.

During the next 2½ weeks the patient received 25 mg. of testosterone and 5 mg. of desoxycorticosterone daily. She was given 2000 cc. of Amigen with 300 cc. of 50 per cent glucose intravenously daily, and was eating well. She appeared to be definitely improving. The blood pressure varied between 95/55 and 100/65. The nonprotein nitrogen had fallen to 60 mg. per 100 cc., and the chloride had risen to

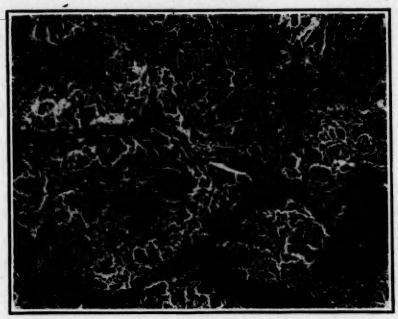

FIGURE 1. *Photomicrograph of Spleen Showing Marked Deposition of Amyloid.*

100 and the sodium to 136 milliequiv. per liter; the carbon dioxide combining power was 22.3 millimols per liter, and the lactic acid was 2.8 mg. and the phosphate 5.7 mg. per 100 cc. The plasma reaction was pH 7.38.

During the next 2 weeks no desoxycorticosterone or testosterone was given, but Amigen and glucose were continued. Ankle edema appeared for the first time, and vomiting began. The nonprotein nitrogen rose to 116 mg. per 100 cc., and the blood pressure fell to 84/44. Adrenocortical extract, desoxycorticosterone and testosterone were resumed. During the next 24 hours, however, the patient gradually became more and more dyspneic and began to have definite air hunger. It appeared to most observers that she was having tracheal obstruction at the site of the tracheotomy scar rather than dyspnea secondary to acidosis. Consequently, tracheotomy was repeated, with some transient relief. No definite obstruction was found at operation. The nonprotein nitrogen had risen to 143 mg. per 100 cc.; the chloride had fallen to 87; and the sodium to 130 milliequiv. per liter, and the carbon dioxide to 13 millimols per liter. The blood pressure fell further to 70/30. The patient died 12 hours later.

Autopsy. Post-mortem examination was performed 14 hours later. The body was that of a well developed, thin Negress. Scattered areas of granulation tissue were present on about 2 per cent of the body surface. The most striking findings were in the spleen, liver, kidneys and adrenal glands.

The spleen weighed 240 gm. It was firm, and the cut surface was pale rose in color and dotted with pale, translucent areas about 1 mm. in diameter. The architecture of the spleen was markedly altered. With the lowest magnification a section appeared to be composed almost completely of a homogenous red substance, with only scattered small zones of remaining splenic pulp. Under higher magnification, the red areas were seen to be malpighian corpuscles largely replaced by amyloid (Fig. 1), a splenic artery being found with each area. This substance was arranged in irregular masses and gave a positive reaction for amyloid when stained with Congo red.[3] Isolated cells and small groups of cells, consisting of lymphocytes and rarely red cells and polymorphonuclear leukocytes, lay between the masses of amyloid. The wall of the arterioles usually merged imperceptibly with the surrounding amyloid. In the areas of remaining splenic pulp, numerous red cells, a slightly increased number of polymorphonuclear leukocytes and macrophages containing golden yellow pigment were found. The walls of sinusoids and small arterioles and trabeculae were widened and appeared red and acellular, being composed principally of amyloid.

The liver weighed 1925 gm. The liver was congested and edematous and contained some amyloid. The degree of amyloidosis, however, was considerably less than that in the spleen and varied from section to section. Amyloid was found in the walls of small arterioles and larger arteries of the periportal areas. In widespread areas amyloid was found lying as large homogenous red masses between the sinusoidal lining and the hepatic cells. The hepatic cells were compressed in some areas. Amyloid was also found in the walls of large veins, lying just below the endothelium. The bile ducts were not involved. In areas not involved with amyloid the sinusoids were widened and filled with blood, and the liver cords compressed. Edema was suggested by the presence of a narrow space between Kupffer's lining and hepatic cells; pink granules were visible within this space in some places.

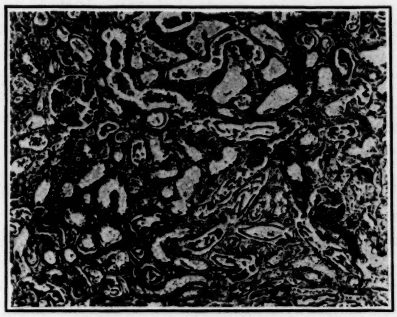

FIGURE 2. *Photomicrograph of Kidney, Showing Widespread Deposition of Amyloid.*

The combined weight of the kidneys was 400 gm. The capsules stripped easily from a smooth surface. The cortices were mottled purple and yellow and measured 0.7 to 0.8 cm. in thickness. They were poorly demarcated from the medullae, which were of a purple hue nearest the cortices and pale at the pyramids. There were six yellow stones measuring 2 to 3 mm. in diameter within the left pelvis. In addition, there were small yellow granules of sand in the same pelvis. There were three similar stones in the right pelvis. The mucosa of the pelves and calyxes were moderately injected. There was no exudate. The ureters and pelves were not dilated. The kidneys showed extensive amyloidosis. There was universal and marked amyloidosis of the glomeruli, interstitial vessels and tubules. The walls of the afferent vessels of the glomeruli were thickened and, for the most part, red and amorphous. Large masses of amyloid were present in the interstitial tissue and capillary walls of the glomerular tufts, resulting in narrowing and obliteration of the capillaries. The basement membrane of Bowman's capsule showed hyaline thickening. With few exceptions every artery or arteriole showed thickening of the walls with amyloid (Fig. 2). In many vessels the lumen was obliterated. The veins were only occasionally and irregularly involved. There was amyloidosis of the tubules. This was not extensive and appeared for the most part in

the medulla. The amyloid was found in the region of the basement membrane of tubules. The tubules, however, showed striking changes in addition to the presence of amyloid. In many convoluted tubules some cells were swollen, pale and granular, whereas others were vacuolated and distended and appeared lace-like. The cells were often ruptured, and the lumen of the tubules was often filled with pink cytoplasmic debris. No fat was demonstrable with sudan IV stain. Other convoluted tubules were widely distended, and the epithelium was flattened. No mitotic figures were seen. A few of the convoluted tubules contained polymorphonuclear leukocytes, and others contained masses of cellular debris. No hyaline casts were found. The interstitial tissue was congested. A few small foci of lymphocytes were present.

In the pancreas amyloid was found in the walls of the arterioles of the interstitial tissue. Arterioles of an occasional islet also contained amyloid. The islet and acinar tissue was unchanged.

The pituitary body was of normal size. Sections of the anterior lobe and pars nervosa showed amyloid within the walls of arterioles and in the walls of some veins. There was no apparent change in the cells of the anterior lobe.

The combined weight of the adrenal glands was 30 gm. The left cortex was of normal thickness and of a pale yellow color; the right was thin, shell-like and pale yellow. Both medullae were brown. The two adrenal glands were similar histologically. With lowest power the glands appeared to be almost totally replaced by homogenous, red-staining amyloid, with the exception of a very narrow zone just beneath the capsule and the innermost cells of the reticularis and the medulla. The outermost cells of the zona glomerulosa were distinct and free of amyloid, and many contained fine vacuoles. These stained faintly with sudan IV. The remainder of the cortex, except for a few clusters of cells of the zona reticularis, contained considerable amyloid (Fig. 3). For the most part the cells and vessels were completely replaced by masses of amyloid. These were scattered short columns of cells where the cytoplasm blended with adjacent amyloid. Short double rows of cells occasionally separated and, forming a tubule-like structure, were found surrounded on all sides with amyloid. The cells of the medulla were relatively unaffected, although the vessels contained amyloid in their walls. Formalin-fixed frozen sections, when examined with polarized light, after warming and slight trauma, showed only a rare doubly refractile body (cholesterol esters). Crushed cortex showed practically no refractile cholesterol esters. Little fat was demonstrable with sudan IV and when found appeared as small droplets within the cytoplasm of the narrow zone of unaffected zona glomerulosa lying beneath the capsule.

This patient with thermal burns developed in the twelfth month a syndrome characterized by profound and progressive weakness, decreased tolerance to barbiturates and general anesthesia, a low temperature, a low blood pressure, a rapid thready pulse, cold clammy extremities, convulsions and coma.

The diagnosis of Addison's disease in crisis was first made on clinical examination alone and was confirmed by the results of laboratory examination, which showed a marked lowering of the serum sodium, chloride and carbon dioxide combining power and an elevation of the nonprotein nitrogen. The diagnosis was further confirmed by the response to the hormonal and salt treatment, after which there was an immediate improvement in the clinical condition of the patient and a gradual return to normal of the sodium, chloride and carbon dioxide combining power and a fall in the nonprotein nitrogen.

Two weeks after specific treatment had been omitted the condition of the patient became worse, with dyspnea, weakness and a fall in the blood pressure as the principal symptoms, and in spite of intensive hormonal treatment the patient died within twenty-four hours. Post-mortem examination disclosed generalized amyloidosis, with particular involvement of the adrenal glands and kidneys.

The abnormalities of the urine and the elevated nonprotein nitrogen can be explained by the extensive amyloidosis of the kidneys. It is also probable that renal failure contributed to the abnormal electrolyte pattern seen in the blood. The results of

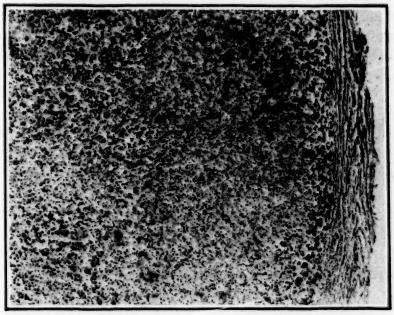

FIGURE 3. *Photomicrograph of Adrenal Gland, Showing Marked Deposition of Amyloid in the Cortex, Chiefly in the Zona Fasciculata.*

these electrolyte studies strongly suggest the retention of fixed acids in the blood. Renal failure, in certain cases, closely simulates Addison's disease.[4]

The insulin sensitivity and the decreased glucose tolerance observed on the first day were probably related to the transient disturbance of carbohydrate metabolism often seen following severe burns and other types of stress.[5] This is borne out by the fact that after the initial period of stress had subsided, the sensitivity to insulin and the glucose tolerance were normal. The sodium and chloride levels and the carbon dioxide combining power were normal on entry.

It is not possible to state categorically the etiology of amyloidosis in this case, which is the only one in which amyloidosis was observed in a series of 60 patients with burns examined at autopsy, many of whom lived several months but none over six months. In addition, a patient with extensive deep burns is still living, with the burns unhealed, after two years who to date shows no evidence of amyloidosis as judged by the Congo-red test. (This patient was discharged well on July 1, 1947, after three years in the hospital.)

It is probable that long-standing infection of the wounds was the chief etiologic factor. Several cultures revealed a hemolytic *Staph. aureus* as the predominating organism, alpha-hemolytic streptococci, diphtheroids and *Pr. vulgaris* also being present

in a majority of the cultures. It has been demonstrated that healing and skin grafting of extensive deep burns proceed more rapidly under conditions of adequate nutrition and that, in the presence of malnutrition, local exudation and presumably local infection of the granulating areas are increased.[6] This patient suffered from long periods of malnutrition during the course of her illness owing to the fact that it was possible to feed her adequately only when special nurses were available. At other times the amount of nursing care available was insufficient, largely because of the universal wartime shortage of nurses. The importance of special nursing care in inducing burned patients to take adequate diets and supplements has previously been emphasized.[7]

On the other hand, it is possible that the intermittent high-protein intake, consisting chiefly of milk, milk powder and Amigen, was a contributing etiologic factor, since feeding of cheese had been reported to cause amyloidosis in animal experiments.[8, 9] At present, however, from the practical point of view, this possibility should be disregarded because of the marked importance of maintaining patients with extensive deep burns in good nutrition and the practical difficulty of administering sufficient protein unless milk and derivatives of milk protein are freely used.

Summary

A case of Addison's disease associated with amyloidosis of the adrenal glands that was part of a generalized amyloidosis following thermal burns is described. The Addisonian syndrome made its appearance a year after the initial injury.

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MEDICAL PROGRESS

WAR WOUNDS OF THE ABDOMEN

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A COMPLETE treatise covering all aspects of abdominal wounds observed in the United States Armed Forces in World War II probably will not be available for several years. On the other hand, many excellent articles on various phases of the problem have recently appeared. It seems worth while to collect and summarize the outstanding contributions that have been published before memories grow dim and interest flags. Obviously, no attempt can be made to include all papers. Nor can extensive considerations of tactical situations, closely related though they are to the care of the wounded, be included here.

The recent surgical care of the wounded differed radically from that in previous wars.† The extent of this change may be gauged by a brief summary of the therapy of abdominal wounds in the past. Interestingly enough, even in the early part of World War I all such wounds were treated conservatively just as they had been formerly.[1] Then a new era in surgery was inaugurated. It became apparent that nearly all patients with such wounds were sure to die unless operated on. Many of the wounded in World War I, however, were not admitted to a hospital for therapy as shown by the fact that of patients admitted to the hospitals only 11 per 1000 suffered from abdominal wounds. In the Fifth Army in the recent war 35 men per 1000 entered with abdominal wounds.[2]

It gradually became apparent that the time lag from wounding to surgical treatment must be reduced to the shortest possible interval if these patients were to survive. This was achieved in the Spanish War by the "three point forward system," described by Jolly,[3] who stated that abdominal wounds represent the best example of the type of case in which the time lag is supremely important for the saving of life. To achieve a reduction in the time lag, the casualty clearing station was divided into a casualty classification post, a hospital for the most urgent cases, including abdominal injuries,

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†Dr. Edward D. Churchill kindly contributed suggestions and data on the subject of initial surgery of battle wounds.

and a second hospital for the less urgent. All three were separated, however, by ambulance transportation involving some delay between the triage center and the first hospital.

The British in the Libyan Campaign in World War II gradually evolved a method that was somewhat similar. The wounded were evacuated from the field dressing station by ambulance. As successive installations equipped for surgery were reached in the chain of evacuation, the most urgent cases were taken from the ambulances and retained for treatment. The selection was often cursory, however, and since the distance between the stations often required many hours of travel, many patients had to be evacuated too far.

The method employed by the United States Army was planned during the North African campaign and was first employed in the invasion of Sicily.[4] Thereafter, it was used throughout the war in the Mediterranean and European theaters. This procedure of triage undoubtedly contributed more to the saving of lives of the patients with abdominal wounds than any other single factor. The method was essentially as follows.

All casualties from the divisional area were collected at the clearing station, immediately adjacent to which a section of a field hospital was established. This institution was staffed by attached surgical teams composed of skillful surgeons, anesthetists, nurses and enlisted personnel with adequate equipment. Thus, even though the team was operating in the most unpleasant and often dangerous situations, the best care could be furnished the soldier at the time when operation was essential. Furthermore, resuscitation and surgery were amalgamated rather than dissociated as they had been in the past. Less urgent cases were sent immediately from the clearing stations to evacuation hospitals by ambulance. Likewise, patients from field hospitals were transferred to evacuation hospitals after initial surgery had been performed and convalescence well established. The dangers of early evacuation of these casualties had previously been shown by the British in the Middle East. Consequently, the field hospital was equipped to care for its patients in the early postoperative period.

Thus, during this war a new mode of treatment of abdominal casualties, based on the following considerations, evolved: the concept that abdominal injuries produce patients who are essentially nontransportable, surgery and early convalescence being transferred to the rear boundary of the division rather than the wounded being sent to the surgeon far in the rear; the principle that resuscitation of patients with abdominal wounds must be rapid and effective, with the result that blood and plasma had to be instantly available in large amounts and surgery became an integral part in the process of resuscitation; the consideration that surgery must be radical and the benefits denied to none; and the concept that proper anesthesia is of the utmost importance if the patient is to survive — the anesthetist is no longer an "etherizer" but must be prepared to cope with all hazards of all types of anesthetics and to play an important part in the resuscitation of the wounded, as well as in the prevention of postoperative pulmonary complications.

New technical details that are of major importance in the management of abdominal wounds also evolved in World War II. The most important are as follows:

The exteriorization of wounds of the colon. Although this maneuver was employed in large ragged wounds of the colon in World War I, its value was not established until World War II. Kirk[5] described it as one of the important surgical advances in this war.

The evolution of an effective method of treatment of rectal wounds. The "retroperitoneal syndrome," with death from extensive infection, was practically eliminated by wide local drainage and colostomy.

The thoracic approach for thoracoabdominal wounds. Dependent on advances in anesthesia, this technic has been almost wholly the product of World War II.

The elimination of enterostomy as a method of treatment of wounds of the small intestine.

Table 1. *Over-All Mortality following Visceral Wounds.*

Site of Wound	Mortality in American Expeditionary Force (1917-1918)	Mortality in British 8th Army (1942)	Mortality in Second Auxiliary Surgical Group (1943-1945)	
	All cases	All cases	All cases	Wounds of single viscus
	%	%	%	%
Colon	60	59	37	23
Jejunoileum	70-75	53	30	14
Liver	66	49	27	10
Stomach	55	20	40	28
Kidney	25-30	65	35	16
Spleen	63	55	24	12
Rectum	45	52	30	14
Urinary bladder	50*	50	30	0
Duodenum	80	—	56	50
Pancreas	—	—	58	100
Gall bladder	—	20	30	0
Ureter	—	—	41	0

*Approximate.

The advances are reflected in various statistics that have appeared. Thus, the over-all mortality of patients with abdominal wounds admitted to American Expeditionary Force hospitals in World War I was 66.8 per cent.[6] The mortality of 381 such cases treated in the British Eighth Army during a three-month period in 1942 was 42.5 per cent.[7] In 2918 abdominal cases that had visceral wounds operated on by the Second Auxiliary Surgical Group in World War II the mortality was 25.5 per cent.[2] These figures do not adequately measure the actual improvement, for in World War I, only less severe wounds were operated on and fewer patients reached

the hospital. Thus, the mortality rate of the Second Auxiliary Surgical Group patients of a character comparable with those of World War I was about 13 per cent. On the other hand, the over-all mortality for all the armed forces will not be so low as that of the Second Auxiliary Surgical Group.

A comparison of the over-all mortality of the wounds of the various viscera in the American Expeditionary Force[1] in World War I and in the British Eighth Army (Libyan Campaign)[7] and the Second Auxiliary Surgical Group[2] in World War II is presented in Table 1. It will be noted that, because of the high incidence of wounds of multiple viscera, the over-all patient mortality is much less than that when the viscera are considered separately.

Several methods have been proposed to estimate the prognosis of the wounded. The most important are the time lag, the depth of shock on arrival in the field hospital and the multiplicity factor. These procedures require further consideration.

The time lag has been investigated by many surgeons, in an attempt to prove the obvious truth that delay in treatment increases the death rate. The variability of war wounds, however, introduces factors that make most such studies worthless. Thus, Brott and Childs[2] found that, if all cases are considered, "the mortality of any unselected groups of abdominal cases at any selected time interval from wounding to surgery is approximately constant." Ogilvie[7] even observed that an increased time lag works both ways, but chiefly toward a lower operative death rate and that delay causes peritonitis but also eliminates the worst cases. Consequently, Brott and Childs studied the mortality when the two variables — the time lag and the number of abdominal organs involved — were separated. These figures show clearly that the death rate rises with delayed treatment. Giddings and McDaniel,[2] studying a series of 355 cases in which the small bowel was the only viscus injured, found the mortality to be 7 per cent if the operation was done within eight hours. The mortality rose to 14 per cent in twelve hours, 22 per cent in twenty-four hours and 30 per cent in forty-eight hours.

The depth of shock is difficult to estimate. Among the important considerations are the level of the blood pressure, the rapidity of the pulse, the pulse pressure, the state of the peripheral circulation as evidenced by cold, pale or cyanotic extremities and signs of cerebral anoxia. Of these features the most reliable, according to Towery,[2] are the trends of the blood pressure and pulse as resuscitative therapy is carried out. Beecher[8] noted that the pulse rate and the amount of sweating are of no value in estimating the depth of shock; on the other hand, the fullness of the pulse and the blood pressure level are of great importance. Since the blood pressure is the most reliable objective criterion of these features, the degree of shock has usually been measured by the level of the systolic pressure. Towery and Welch[2] grouped their patients of the Second Auxiliary Surgical Group in four categories. The degree of shock was said to be profound if the systolic blood pressure on admission was 40 or below, severe from 41 to 70, moderate from 71 to 100 and incipient or no shock from 101 to 120. The mortality in these four groups was respectively 66.4 per cent, 50.4 per cent, 38.0 per cent and 18.1 per cent. These data show clearly that the prognosis may be estimated with some accuracy at the time the patient arrives in the field hospital.

The "multiplicity factor" has been shown to be of extreme importance in the determination of prognosis. This factor, as defined by Wolff, Childs and Giddings,[2] refers solely to the number of abdominal organs injured in a given case as determined at operation. In 2918 cases of abdominal wounds the mortality was 12 per cent if one organ was involved, 27 per cent with two, 46 per cent with three, 60 per cent with four and 88 per cent with five organs involved.

The nature of wounds of the abdomen caused by high-velocity shells has been investigated by Puckett, McElroy and Harvey.[9] Their studies show that the abdomen expands with the penetration of a high-velocity missile. This expansion persists for 1 or 2 milliseconds, and is followed by a constriction that lasts for 4 or 5 milliseconds and is succeeded by a second bulging of the abdominal walls of greater duration but less intensity. Coincident with the initial abdominal expansion there is a large temporary cavity within the abdomen. Internal damage to the viscera is far out of proportion to the wounds of exit and entrance. The general effect is that of an explosion within the abdomen.

The care of the wounded may be classified, according to Churchill,[10] into initial, reparative and reconstructive phases. In terms of Army installations of World War II, this means essentially the care furnished first by the field and evacuation hospitals, secondly by the overseas general hospitals and finally by the general hospitals in the Zone of the Interior. Further discussion of abdominal wounds is divided into these three categories.

Initial Surgery

Abdominal casualties must be evacuated as rapidly as possible to a surgical unit prepared to handle them. Only primary measures of resuscitation, such as plasma administration and the tourniquet control of hemorrhage from accompanying wounds of the extremities, are employed before the patient reaches a surgical installation.

As soon as the patient arrives in the field hospital resuscitation is begun, his clothes are removed, all wounds are inspected, and he is placed on a clean litter. Thereafter, a rapid estimate of his general condition is made, x-ray films are taken, the stomach is lavaged, the urine is examined, pain is alleviated,

chemotherapy is begun, and surgery is instituted. Several of these measures require special consideration.

Resuscitation in abdominal cases involves primarily the administration of blood.[11] Plasma is administered while cross-matching is carried out. Thereafter, if the patient is in shock, 1000 cc. of blood should be given in fifteen to twenty minutes and continued at a slower rate. The average abdominal case requires 1500 to 2000 cc.

The maximum time devoted to preparation of patients should be one and a half to two hours. If at that time there has been no response to treatment the usual causes of persistent shock must be considered. They are, according to Berry,[12] continuing hemorrhage, massive peritoneal contamination, pelvic cellulitis or clostridial myositis, a large evisceration, blast injury of the lungs, heart, abdomen or brain or other severe wounds.

Physical examination is directed especially toward a determination of the course of the missiles. All evidence points to the fact that they pursue straight courses through the abdomen. Any penetrating wound of the chest, back or thigh may represent a possible abdominal penetration. According to Stewart,[13] the most important errors in the preoperative physical examination are failure to examine the rectum and omission of an examination of the peripheral nerves. If the possibility of a rectal wound exists and no blood is found on the examining finger, a proctoscopy must be done.

Auscultation of the abdomen is of value. Jarvis[14] found peristalsis to be uniformly absent with intraperitoneal perforation of a hollow viscus. On the other hand, absence of peristalsis is not diagnostic of perforation. Blackburn and Rob[15] observed peristalsis in the presence of lesions of the hollow viscera in only 5 of 89 cases, whereas in the absence of hollow visceral lesions, peristalsis was present in 64 cases and absent in only 1. Estcourt[16] noted active peristalsis in several patients who at operation were found to have perforation of the colon.

The primary purpose of x-ray examination is to determine the location of retained fragments and thereby to visualize the path the missile has taken.

The stomach tube, preferably one of large caliber, is passed, and the stomach emptied. It is a fortunate event when vomiting is induced by this maneuver.[8] Thereafter, a Levin tube is introduced and maintained during and after operation. Beech and Wolff[17] demonstrated that, with few exceptions, this procedure should be an integral part of the preoperative resuscitative program, regardless of the site of the wound.

If the patient cannot void, a catheter must be passed and the urine examined. If bloody urine is obtained it is better to avoid irrigation of the catheter until the abdomen is opened (Michels[2]).

Pain is more frequent after abdominal wounds than any other type.[18] Consequently, many patients have been oversedated and during the progression of resuscitation have developed acute morphinism. Therefore, it is better to administer morphine by the intravenous route and in comparatively small doses.

Chemotherapy, which is instituted as soon as the patient arrives, usually consists of the intramuscular administration of 25,000 units of penicillin although, when available, up to 100,000 units has been given intravenously. The whole problem of chemotherapy is considered below.

When the patient is ready for surgery or when surgery becomes mandatory because his condition fails to improve, the anesthetic is begun. This should preferably be ether oxygen administered by a closed system through an intratracheal tube. To avoid the deeper levels of anesthesia, local or regional nerve blocks may be added. This is especially true in the upper abdomen, where the intercostal nerves may be blocked. Spinal anesthesia is contraindicated because of the deleterious effect on blood pressure. Pentothal sodium should not be employed as the primary anesthetic agent if there is any likelihood of abdominal penetration, since a long operation with adequate relaxation may be necessary.

The incision should give adequate exposure of the wounded section of the abdomen and should permit secure closure. Thus, if a colostomy may be necessary, the primary incision should be placed well away from the projected site of the stoma. Vertical paramedian incisions are usually preferable. In the upper abdomen, transverse or subcostal incisions may be used. Incisions through the wounds of entrance or exit, and transverse lower abdominal incisions should be avoided.

Ogilvie[7] states that "in the abdominal surgery of warfare technique may be summed up as a simple plan, a purposeful over-haul, and a rapid repair." Usually, on opening of the peritoneal cavity, blood, fecal matter or a mixture of both is encountered. The cavity is emptied of its fluid contents as rapidly as possible. If hemorrhage continues, usually the spleen, liver or large intra-abdominal veins have been wounded. Primarily, bleeding is controlled. Wounds of the abdominal wall should be carefully inspected, since they may furnish the site of the hemorrhage. Thereafter, the source of fecal contamination is determined. The colon is examined first, and any wound carefully walled off. The small bowel and stomach are observed in that order, and, finally the other viscera. When the entire damage has been ascertained, the various wounds are repaired.

Visceral Wounds

The incidence of involvement by organs in 2918 patients with visceral wounds received by the Second Auxiliary Surgical Group was as follows: stomach, 13.2 per cent; duodenum, 3.7 per cent;

jejunum and ileum, 37.0 per cent; colon and intraperitoneal rectum, 35.0 per cent; extraperitoneal rectum, 4.9 per cent; liver, 26.7 per cent, gall bladder and bile duct, 1.7 per cent; spleen, 10.8 per cent; kidney, 13.4 per cent; ureter, 0.8 per cent; urinary bladder, 4.9 per cent; pancreas, 1.9 per cent; and major abdominal vascular injury, 2.4 per cent.[2] The over-all mortality rate in this series was 25.5 per cent, varying from 26.6 per cent in winter to 19.7 per cent in summer. It was found that children and the aged wounded civilians withstood operative procedures poorly. Of the deaths, 48 per cent occurred on the day of operation, and 62 per cent within seventy-two hours. The causes of death were listed as shock (62.4 per cent), pulmonary complications (12.8 per cent), peritonitis (12.0 per cent), anuria (4.6 per cent), anaerobic infection (1.6 per cent), miscellaneous (4.0 per cent) and unknown (2.5 per cent).

Wounds of the following viscera are briefly considered.

Stomach. Wounds of the stomach may be suspected preoperatively if blood has been vomited or aspirated through the nasal tube. The course of the missile in the series of the Second Auxiliary Surgical Group was thoracoabdominal in 47 per cent of cases, and abdominal alone in 53 per cent. Bolman and Caul[19] point out that the perforation may be entirely intrapleural, so that abdominal signs are entirely absent. It is clear that unless every possible penetrating wound of the diaphragm is explored, many of these wounds will be overlooked. The perforation of the stomach is often difficult to locate, especially if the abdominal approach is necessary and the laceration is high on the greater curvature. It is well to remember, as in all other wounds of the gastrointestinal tract, that unless the foreign body is found within the lumen of the viscus, there must be an even number of perforations, barring tangential lacerations.

Closure of the stomach should be by a careful two-layer suture. Purse-string sutures should be avoided, since secondary hemorrhage is more frequent from the stomach — because of its extraordinary vascularity — than from any other part of the gastrointestinal tract. No data can be offered concerning the merit of absorbable or nonabsorbable sutures in any part of the gastrointestinal tract. Many surgeons had more confidence in an outer layer of cotton or silk because of the established peritonitis present in most of the cases. Other surgeons used catgut throughout.

Duodenum. In the great majority of wounds of the duodenum, the wound of entrance is in the right upper quadrant or in the back, posterior to the duodenum. The mortality is high because other viscera are frequently damaged. Accurate exposure of the retroperitoneal duodenum requires mobilization of the hepatic flexure of the right colon and section of the lateral attachments of the duodenum. In this manner the entire organ may be inspected. Repair is effected either by a two-layer closure or by resection and anastomosis.

If the patient survives the first few postoperative days, a fistula will form unless the closure has been satisfactory. In 20 cases in which transections were observed in the Second Auxiliary Surgical Group, only 6 patients lived through the sixth postoperative day, and fistulas developed in 2.

Jejunum and Ileum. The small intestine is wounded oftener than any other abdominal viscus. Perforations are usually multiple and, because the ileum is longer than the jejunum, are more frequent in the former. It is essential to inspect all wounds of the intestine before repair, since if a resection is necessary other wounds may be included in the excised segment. Repair is either by suture or by resection and anastomosis. A two-layer end-to-end anastomosis is usually the procedure of choice, if resection is to be done, since it can be made more rapidly than a side-to-side anastomosis. It must be made with care to avoid late obstruction at the anastomotic line.

The individual surgeon must decide which procedure is to be employed. The British have recommended resection only as a matter of last resort. It was used much more frequently in United States Army hospitals. The essentials are first that all traumatized areas must be repaired and secondly, that the remaining blood supply must be adequate. Thus, any segment of intestine from which the mesentery has been detached for 5 cm. or more should be resected because gangrene and perforation will occur later if it is left in situ. One resection can frequently dispose of several lacerations and severely traumatized bowel; in my opinion, this is more satisfactory than leaving areas of questionable viability that may perforate at a later time. Severe damage to the mesentery will also require surgery. It is to be expected that the mortality after resection will be higher than that after suture, because more serious injuries are included. Thus, Giddings and McDaniel[2] found in 1117 cases that the mortality following suture was 23.3 per cent and that after resection, 37.3 per cent.

Under no circumstances is an enterostomy desirable, except as noted below in wounds of the cecum. The depletion from rapid loss of secretions of the upper intestine is formidable. Fortunately, recourse to enterostomy was rare in World War II.

An interesting postoperative complication was reported by Hawkes and Spencer.[20] Following a thoracoabdominal wound with perforation of the upper small intestine and colon, there was massive bleeding from the colostomy. A total of thirty-five transfusions was employed. Twenty-two days after the injury, exploration revealed hemorrhage from an artery at the site of the closure in the jejunum. Resection was followed by recovery.

Colon. The treatment of wounds of the colon has provoked more discussions than that of injuries to any other viscus. From a mortality of about 60 per cent in World War I, the death rate has been nearly halved, particularly because of the widespread adoption of the principle of exteriorization. The method, however, varies depending on the section of colon that is wounded.

It is important, in a discussion of wounds of the colon, to differentiate clearly three types of surgical procedures. In the first group a perforation of the bowel is discovered; the loop is exteriorized, and the "colostomy" has already been made by the missile. In a second group, there is extensive soft-tissue damage to the buttocks or a wound of the low sigmoid, but a careful suture of the perforation of the colon is possible; in these cases the sigmoid is exteriorized, and a small incision is made for temporary decompression that may be converted into a defunctioning colostomy by complete transection should it be needed. In the third group extensive wounds of the lower bowel, bladder or pelvis require a true colostomy that will entirely defunction the distal segment.

There are certain essential features in any colostomy. It should be placed in a separate incision from that employed for the laparotomy. Usually, a small muscle-splitting incision can be made. Wounds of entrance or exit should be avoided unless they are small, because of the increased chance of sepsis or breakdown. Adequate mobilization is most significant. The forward surgeon should remember that postoperative abdominal distention will shorten the colostomy and invite retraction into the abdominal wall. Most of the complications referable to colostomies observed in the overseas general hospitals could have been avoided if a proper site had been chosen for the colostomy, and the bowel widely mobilized.[21]

Colostomies are either of the loop or of the spur type. Acrimonious discussion was often heard from the partisans of both types in the overseas hospitals. Later, some surgeons working in the general hospitals of the Zone of the Interior advised complete division of both limbs of all colostomies to avoid any spill-over of feces from the upper to the lower segment. To the impartial observer, it seems that all these procedures have their indications.

The whole problem has been ably discussed by Mason,[22] who divides these wounds into the following groups: perforation of the antimesenteric portion up to half the diameter of the segment, which is best treated by a simple, no-spur, loop colostomy; perforations of the mesenteric border and of the antimesenteric border larger than half the diameter, which should be treated by a double-barrel spur colostomy; severely torn segments and complete transections, which also require a double-barrel spur colostomy; injuries to the mesentery producing nonviable segments, which are treated in the same way; a sixth group, which includes the first five groups but in the injury to the rectosigmoid just above the peritoneal floor, in which repair must be effected and a loop colostomy done proximal to the injury; a seventh group, which includes the first five groups occurring in the rectum between the pelvic peritoneum and anus and in which Mason advises a loop colostomy; and injuries of the right portion of the colon necessitating right colectomy or cecectomy, which are probably best treated by a spur ileocolostomy. In addition, Mason states that areas of questionable viability may be exteriorized. Any perforation in an exteriorized segment may be closed; occasionally, the suture will hold.

Disagreement with the above conclusions will occur chiefly in the seventh and eighth groups. The rectal wounds are considered below, but it is necessary to discuss injuries of the right portion of the colon more fully here.

Wounds of the antimesenteric margin of the ascending colon may be converted into tube cecostomies. Small perforations without contusion of the bowel may be closed primarily by experienced surgeons. A large rubber tube is employed and is withdrawn in four or five days. If there is a small posterior wound of the cecum as well, it may be closed by suture; it is always important to mobilize the whole ascending colon to disclose such perforations.

A more difficult problem arises when there has been extensive damage to the ileocecal area and this whole segment must be resected. There are several ways of handling the bowel. Primary ileocolic anastomosis has occasionally given brilliant results, but is not recommended as a routine procedure, since the peritonitis produced by wounds of the ascending colon is the most virulent from all colonic injuries. A spur-type ileocolostomy may be done, the stoma being brought out in a separate incision. The profuse ileal drainage will be difficult to handle, serious problems in wound healing arise, and even deficiency states may appear quickly. Many surgeons followed this technic to the end of the war, holding the patients in the forward hospital for early (three or four days) crushing of the spur. This difficulty may be obviated by a side-to-side ileocolostomy, either the distal ileum or the proximal colon, or both, being brought out for decompression. A final suggestion is an ileocolostomy with wide separation of the two limbs.

The experience of the Second Auxiliary Surgical Group is of interest in this regard. The conclusions of Chunn and Hauver[2] were as follows:

> Wounds of the ascending colon presented a particularly difficult problem when it was necessary to resect the entire right colon and terminal ileum. Early in the war the most popular procedure was the resection and double-barrel ileocolostomy. This procedure was not satisfactory and carried a mortality rate of 64.7 per cent. Later on, resection and ileocolostomy anastomosis and either double mucous fistulae or single mucous fistula was advocated

and was done with some improvement in the mortality rate. However, this mortality rate remained high at 51.7 per cent. Two patients with resection of a portion of the ascending colon had the proximal and distal ends exteriorized and both patients died.

If a loop colostomy is to be made, the loop may be supported by a glass or rubber tube. If a spur colostomy is made, the spur should be made 15 cm. long, and it should project 5 cm. above the skin. The spur should be formed by two catgut sutures along the antimesenteric margin. The bowel should be opened on the operating table if the perforation is distal to it. In other cases it may be advisable to leave the clamp on for twenty-four hours until the wound is well sealed off.

Rectum. Wounds of the rectum are characterized by difficulty of diagnosis, inaccessibility, frequent damage to other structures, and the hazard of retroperitoneal infection. Laufman[23] notes that the missile may enter anywhere from the costal margin to the lower thigh. Only 6 per cent of patients with buttock wounds in his series had rectal perforations. The patient usually escapes injury to the rectum unless the missile crosses or is lodged near the midline. Patients with unsuspected and untreated rectal wounds are likely to die of profound toxemia.

When a rectal wound is present or suspected, the posterior wound should be débrided before the laparotomy is done, unless active intra-abdominal hemorrhage demands initial laparotomy. This will require adequate exposure of the tract of the missile, as well as exposure of the rectum through an anococcygeal incision that must be deepened through the fascia propria of the rectum. The coccyx will frequently need to be moved to secure wide drainage. If so, because of the possibility of osteomyelitis of the lower sacrum, as noted by Colcock,[24] the bone should be cleanly removed and the sacrococcygeal cartilage excised. The rectal wound is exposed. Closure is advocated by Croce, Johnson and Wiper[25] and Mason,[22] even though the chances of failure are high. The wound is packed lightly.

Laparotomy is then performed. If the rectal wound is small and uncomplicated a sigmoid colostomy with separation of limbs is wise. If there is extensive damage to bony pelvis and bladder, the colostomy should be made in the transverse colon.

A rectal wound is often first diagnosed at laparotomy. A retroperitoneal hematoma arising from the pelvis usually indicates damage to the rectum, and a colostomy should be performed accordingly.

Morgan[26] lists some of the complications that have been observed — namely, osteomyelitis, meningitis following removal of a shell fragment near the sacral canal, diphtheritic infection and secondary hemorrhage.

(*To be concluded*)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

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CASE 33311

PRESENTATION OF CASE

A twenty-four-year-old man was admitted to the hospital because of pain in the back.

Two weeks prior to admission the patient noted a steady dull aching pain in the right flank, lasting about five or six hours and then subsiding. Four days later it recurred in the left flank, and subsequently he was never free from pain in either the right or left flank. The pain radiated to the front of the abdomen, was sometimes made worse by deep breathing, caused anorexia and at times prevented sleep. He had taken fluids without vomiting. He had noted an evening rise in temperature since the onset of the pain. On the day of admission he hiccuped continuously.

Since the age of eight the patient had noted increasing muscular weakness. Early there was a contracture of the toes, so that walking was possible only on the toes. Because of increasing weakness of the legs walking had been impossible for the past eight years, and by the time of admission the trunk and upper extremities were so weak that the patient could not lift his arms to shoulder level and could not arise in bed without aid. One year before entry he had suffered from palpitation, breathlessness and swelling of the legs. His physician told him that he had high blood pressure and gave him digitalis, which afforded considerable relief.

His parents were living and well but one brother out of five siblings and a maternal cousin suffered from similar muscular weakness.

The patient appeared too acutely ill to permit extensive examination. He was obese, and the muscles were generally weak, although they appeared and felt hypertrophied, especially the calf muscles and biceps. The lower extremities were cold, livid and pulseless. The fundi were poorly visualized but revealed narrowed arterioles. The throat was slightly injected. The chest was clear. A forceful apex impulse was felt 3 cm. beyond the midclavicular line, and a Grade I systolic murmur was audible at the apex. The pulmonic second sound was considerably louder than the aortic. The abdomen was distended and tympanitic, with diminished peristalsis. There was tenderness in the right costovertebral angle and right flank and to a less extent in the left costovertebral angle. There was extreme weakness of all extremities, with equinus deformities of the feet and hypertrophy of the calf tissues.

The white-cell count was 15,800, with 92 per cent neutrophils; the red cell count was 5,100,000, with 15 gm. of hemoglobin. The urine on two occasions gave a ++++ test for albumin, and the sediment showed occasional hyaline and granular casts and, on one examination, 30 to 40 white cells and 2 to 3 red cells per high-power field. X-ray films revealed enlargement of the heart, particularly in the region of the left ventricle. The cardiac apex lay within a fingerbreadth of the chest wall. There was questionable notching of the ribs. The aorta could not be traced. The lungs were clear. There was an area of translucency between double contours of the right leaf of the diaphragm.

The temperature rose from normal on admission to 103°F. in the afternoon and fell to normal again by the following morning. The pulse was around 120, and the respirations about 20. The blood pressure was 110 systolic, undetermined diastolic.

Hiccups continued the day after admission, and the patient complained of some shortness of breath. The nonprotein nitrogen was 54 mg. per 100 cc. Later that day he was found to be breathing in Cheyne–Stokes rhythm; the neck veins were distended, and the pulse was 120, with an audible gallop. He was cold and sweaty, and the blood pressure was not obtainable. The chest was clear to percussion and auscultation. Later in the morning he improved; the blood pressure was 90 systolic, 70 diastolic, and the pulse was still 120, and the breathing was regular. An electrocardiogram was not remarkable, except for evidence of some degree of bundle-branch block. By evening the respiratory difficulty had again developed, without evidence of fluid in the chest. He expired at 1:00 the following morning, forty-eight hours after admission.

DIFFERENTIAL DIAGNOSIS

DR. MARIAN ROPES: To me this picture is extremely confusing. Many systems are involved, and it is difficult to find the interrelation between the diseases. The predominant involvement is in the neuromuscular, cardiovascular and renal systems, with possible or probable gastrointestinal-tract involvement. The neuromuscular involvement was of sixteen years' duration and consisted of progressive muscular weakness. There are various causes of such a condition that one must think of. Myasthenia gravis is the first, for which I find little evidence. There is no evidence for dermatomyositis. I think that the likeliest explanation for such a steady progressive muscular weakness with some disproportion in the size of muscles is myopathy — muscular dystrophy. If this is the cause of the muscle disease, there is no evidence that it is related to the terminal illness, which began two weeks before death. It

would be intriguing to try to link them together, but the only possible way that I can is by some involvement of the vascular system, presumably an anomaly of some kind. On admission the legs were cold and pulsations could not be felt. There was also questionable notching of the ribs. It seems probable to me that the majority of the changes in the legs were of acute onset and related to the terminal illness. Whether or not he had any alteration of blood supply to the lower extremities before the last two weeks is difficult to say. Perhaps at this time the x-ray films would help us out, especially in regard to the questionable notching.

DR. STANLEY M. WYMAN: The films could not be found for demonstration here, but I remember that we argued about them at some length. It was the majority opinion that they were not true notches, since they all occurred at the same area in the rib.

DR. ROPES: That is disturbing because there are two differential points that I had hoped the x-ray films could help us with. One was the question of notching. If notching was present, coarctation should be seriously considered.

The second question is whether or not the area of translucency was definite enough to conclude that there was air under the diaphragm. Apparently we are not going to have the opportunity to look at the films to see if it was impressive enough to include rupture of a viscus as one of the possibilities.

To return to my attempt to see if in any way the neuromuscular disease can be linked to the terminal illness, vascular anomaly has to be considered. Coarctation alone would not, to my mind, explain the weakness involving the upper extremities. Progressive weakness and atrophy of all extremities can occur with hypoplasia of the aorta. This may be found with a large or small heart, and it is usually associated with accentuation of the pulmonic second sound, which was present here. The course of such a condition, however, is slowly progressive congestive failure. I see no evidence of such progressive congestive failure in this case. I doubt that hypoplasia of the aorta could explain all this picture and therefore it is not a way of linking the neuromuscular disease to the terminal disease.

To turn to the final illness of two weeks' duration, I find three possibilities that have to be seriously considered. The first is rupture of a viscus, which I have mentioned. The seriousness with which we consider this depends to some extent on whether or not there was air under the diaphragm. If rupture occurred, I doubt that it happened at the time of onset of symptoms, two weeks before admission. It is much likelier that infarction occurred at that time and then, eventually, rupture. I should expect, however, more evidence of peritoneal irritation at some time during the course than is apparent here. The terminal episode would presumably have to be explained by some secondary event, such as pulmonary embolism.

Another group of events, which I considered as one of the possible explanations, is embolism, pulmonary or renal, or both. There is little definite evidence for pulmonary embolism anywhere in the story. The increased pulmonary tension is suggestive evidence, but surely not more than that. The location of the pain — in the flanks and abdomen — is unusual for that associated with pulmonary emboli. Again if one considered that pulmonary emboli occurred in this patient and were the cause of the terminal episode, one would have to introduce other factors to explain certain findings, such as the renal disease. That could have been caused by pre-existing renal disease or by emboli to the kidneys with infarction. There is absolutely nothing in the history to indicate the former unless one considers the slight suggestion of arterial narrowing as suggestive. The pain is surely consistent with the latter diagnosis, but the location is utterly consistent. In regard to the source of such emboli in the systemic circulation, I find it necessary to introduce the possibility of infection, either on an abnormal aortic valve, for which there is little evidence, or coarctation, if such exists. The laboratory evidence in this case is of little help in differentiation. We have evidence of leukocytosis, with a polymorphonuclear reaction, and fever. If one considered renal emboli as the initial episode one would have to introduce something else to explain the cause of death — such as a pulmonary embolus or disease in the aorta.

The third possibility is a dissecting process in the aorta. If this were present, one would see it in a patient of this age only in the presence of some vascular anomaly. It could occur in a person with coarctation of the aorta, in which case the final dissection and rupture could reach the pericardium and cause pericardial tamponade. In this respect it would be helpful to know that there really had been a sudden cardiac enlargement. That is something we cannot know, however. The final picture, I think, is consistent with bleeding into the pericardium.

In reconsidering the total picture, I find it difficult to differentiate these three groups of possibilities, for which there is little evidence. So far as I am concerned it is a choice between three types of possibilities, no one of which satisfactorily explains all aspects of the picture. I neglected to say that, had dissection occurred from coarctation of the aorta, it is conceivable that increased obstruction to flow could have caused decreased blood supply to the legs and kidneys, with infarction explaining the renal findings. So if I still must choose between these three groups in the absence of being able to determine which is the likelier, I will place first the uncommon possibility, namely, coarctation of the aorta, with subsequent dissection and rupture. The possibility of superimposed infection cannot be ruled out. I think the best explanation of the

neuromuscular findings is muscular dystrophy, although it is intriguing to attempt to conceive that this whole process was related to generalized vascular disease or possibly to a vascular anomaly.

DR. WALTER BAUER: How tall was this man? How much did he weigh?

DR. TRACY B. MALLORY: He weighed 210 pounds. He looked like a powerful man, around 6 feet tall.

DR. ROPES: I was thinking of a small person, I must admit.

DR. BAUER: How many white-cell counts were done?

DR. MALLORY: Only one is recorded.

DR. BAUER: Were there any eosinophils in the smear?

DR. MALLORY: No.

Dr. Taylor, do you want to give us the impression on the ward?

DR. ISAAC TAYLOR: I saw the patient in the Emergency Ward. He presented the picture of shock and severe pain in the back, in addition to what appeared to us to be muscular dystrophy.

DR. BAUER: Where in the back?

DR. TAYLOR: In the right costovertebral angle radiating around the right flank toward the inguinal region.

At that time he gave a history of having been in congestive failure one year previously, and in response to pointed questioning he said that the doctor had told him that he had high blood pressure. He was placed on digitalis and maintained a normal pressure until shortly before admission. The impression in the Emergency Ward was that he was suffering from congestive failure, which accounted for the low blood pressure in the face of a history of high blood pressure. The x-ray films of the lungs were clear, showing no evidence of congestion.

DR. BAUER: What were the signs of congestive failure?

DR. TAYLOR: Cyanosis and respiratory distress. The enlargement of the heart on x-ray examination was quite marked, with a prominent left ventricle.

DR. BAUER: Did the pain radiate anywhere other than to the anterior abdominal wall? Did it go to the legs?

DR. TAYLOR: No. It radiated from the right costovertebral angle around the right flank to the inguinal region. It did not go into the testicles or legs.

DR. BAUER: Were the heart sounds distant or faint? Was there a gallop rhythm?

DR. TAYLOR: The heart sounds were of good quality. I heard no gallop.

DR. MALLORY: Dr. Ropes, do you care to say anything more?

DR. ROPES: I think not.

DR. BAUER: I am tempted to suggest another possibility on the basis of the white-cell count, which was 15,000, with 92 per cent neutrophils, and a temperature of only 101°F. The count seems out of proportion to the degree of fever. In bizarre cases such as this, these findings should always cause one to entertain the possibility of periarteritis nodosa. I believe that periarteritis nodosa with an aneurysm or two could explain everything this man had. On first reading the case, I wondered about congenital hypoplasia of the vascular system. This man's size and weight are against that diagnosis, however. I take it that he had pseudohypertrophic muscular dystrophy, particularly with the family history. Just to throw in another red herring, I shall say that the diagnosis was periarteritis nodosa, with a few mycotic aneurysms, one of which may have ruptured.

CLINICAL DIAGNOSES

Progressive pseudohypertrophic muscular dystrophy.
Coarctation of aorta.
Glomerulonephritis?

DR. ROPES'S DIAGNOSES

Muscular dystrophy.
Coarctation of aorta, with dissection and rupture into pericardium.
Renal infarction?

ANATOMICAL DIAGNOSES

Pseudohypertrophic muscular dystrophy.
Fibrosis of myocardium.
Cardiac hypertrophy and dilatation.
Mural thrombi: left ventricle.
Infarcts of spleen and kidneys.

PATHOLOGICAL DISCUSSION

DR. MALLORY: Although this was the type of case in which we should have liked to do everything, the post-mortem examination was limited to an abdominal incision. I believe that we have most of the answers, however. The heart was greatly hypertrophied, weighing 600 gm. There was no coarctation of the aorta, but the aorta was extremely small, measuring only 4.5 cm. in circumference. The lungs were congested and showed no infarcts. There were no pulmonary emboli. The cause of the flank pain was quite obvious when we looked at the kidneys. The right kidney was totally infarcted, apparently in two stages, since the upper pole was yellow whereas the lower one was grayish red. The right renal artery was completely occluded by a thrombus. The left kidney, which was larger than the right, showed a single large infarct. The left renal artery was patent. The liver showed marked chronic passive congestion, with necrosis of the cells in the central half to two thirds of the lobules. The spleen was enlarged, firm and congested and weighed 400 gm. We believe that there was adequate anatomic evidence for a diagnosis of cardiac failure. Whether the immediate mechanism of death was renal, cardiac or peripheral circulatory failure is impossible to decide on anatomic grounds.

The skeletal muscles showed almost complete replacement with fat tissue in many areas; in other fields the muscle fibers persisted but were most abnormal. Some were hypertrophied, and others extremely atrophic (Fig. 1). There were foci of fibrosis. The picture was typical of pseudohypertrophic muscular dystrophy.

FIGURE 1.

There have been a number of reports of severe sclerosis of the myocardium in patients with muscular dystrophy. The heart showed extensive patches of fibrosis throughout the myocardium, and the muscle cells themselves showed fresh patches of acute degeneration. Also there was considerable infiltration of fat tissue, not uncommon in elderly people but most unusual in a man twenty-four years old (Fig. 2). I believe that we have the right to assume that this myocardial change is part and parcel of the muscular disease.

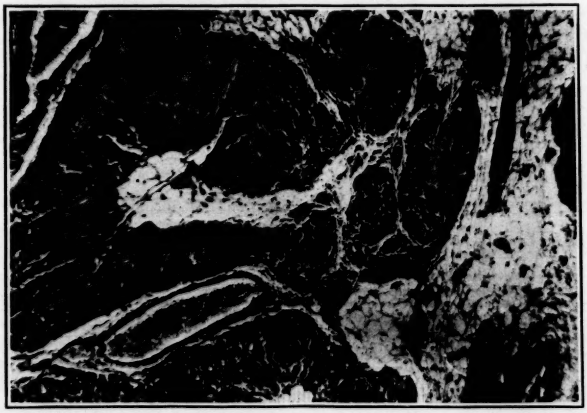

FIGURE 2.

DR. EDWARD F. BLAND: Did he have mural thrombi?

DR. MALLORY: Yes; on the wall of the left ventricle lying between the columnae carneae. They were evidently the source of the emboli.

DR. BAUER: Did he have auricular fibrillation on entry?

DR. MALLORY: I think that the rhythm was normal. The thrombi here were ventricular rather than auricular, as they would be in auricular fibrillation.

DR. BAUER: Was there any vascular disease?

DR. MALLORY: No.

DR. BAUER: Can you tell us more about this type of heart?

DR. MALLORY: So far as I can recall, it is the only one that we have seen.

DR. BAUER: Tell us what others have seen.

DR. MALLORY: Globus[1] was the first person to report this condition carefully, as far back as 1918. Since that time various single cases have been reported, and Bevans[2] recently reported a pair of cases, with extensive atrophy in the myocardium and with fibrosis and with fatty infiltration, corresponding exactly to what was seen here. These changes are sometimes visible in gross, sometimes microscopically.

DR. BAUER: Do these patients have hypertension?

DR. MALLORY: I do not know.

DR. BAUER: I followed a fairly large group of cases of muscular dystrophy with Dr. Aub at the time when they were being treated with adrenocortical extract. A few of these patients are still being seen, but I never happened to see one with this type of heart disease. Have you any idea how often it occurs — in 1 per cent, 20 per cent or 50 per cent?

DR. MALLORY: I have seen no figures.

DR. BAUER: It must be reasonably rare, because some of the people we followed are now well over forty years of age.

DR. MALLORY: Dr. Walter Timme, in the discussion of Dr. Globus's paper, stated that this was commoner in people with acute progressive disease and who died relatively early in life than in those with the slowly progressive type; he did not give any figures, however.

DR. BLAND: Were electrocardiograms made in your cases, Dr. Bauer? The electrocardiogram on the case we are discussing showed no abnormality, except bundle-branch block, which is misleading.

DR. MALLORY: There has been a note in several cases that the electrocardiographic changes were slight or entirely absent.

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CASE 33312

PRESENTATION OF CASE

A sixty-five-year-old unmarried woman entered the hospital complaining of abdominal cramps.

For one year the patient had noted that she tired easily. Three weeks before entry to the hospital she had had some mild cramps in the lower abdomen. Five days before admission the pain recurred; it became worse the next day and continued until she entered the hospital. For forty-eight hours prior to entry, the crampy pain was constantly present. For three days the patient had vomited repeatedly. Nothing had been passed by rectum for four days. The patient had not urinated for two days.

The patient denied previous melena, diarrhea, constipation and genitourinary symptoms. She did state that many years previously she had had some sort of abdominal pain, which was in the midlower abdomen and spontaneously disappeared. She had had no abdominal operations.

The patient appeared acutely ill. The extremities were cold and clammy. The heart and lungs were essentially normal. The abdomen was protuberant, tense, exquisitely tender and tympanitic throughout. A fluid wave was present. Peristalsis was diminished. No spasticity or masses were present. Rectal examination revealed a small uterus and marked tenderness on motion of the uterus; no masses were felt.

The temperature was 99°F., the pulse 140, and respirations 24. The blood pressure was 130 systolic, 70 diastolic.

The white-cell count was 31,700, predominantly neutrophils. X-ray films of the chest showed a normal heart. There were linear areas of increased density at the left base. An abdominal film showed no dilated loops. There was free air beneath the right half of the diaphragm, which was high, and there was a suggestion of gas within the liver.

An abdominal tap on the day of entry produced cloudy, yellow, odorless fluid containing many pus cells and numerous gram-negative bacilli and cocci on smear. A transfusion was given, and gastric suction instituted. The temperature rose to 102°F. and the patient appeared to sink into circulatory collapse; she died on the morning after admission.

DIFFERENTIAL DIAGNOSIS

DR. GORDON A. DONALDSON: One might guess from the length, breadth and depth of this history, particularly the past history, that this patient had entered the Emergency Ward unaccompanied by anyone who might have aided her in giving an account of herself. I got the impression on second reading that she was practically in extremis on admission and that diagnostic studies were strictly limited.

It is quite obvious that she had an overwhelming peritonitis and was in shock therefrom — and even-

tually died of peripheral circulatory collapse. The single blood-pressure reading is in discord with such a picture but may represent a relative hypotension in this patient. The abdomen was protuberant and tense, compressing the lower lung fields. Although no spasm is reported, the abdomen was exquisitely tender, and the lack of reflex spasm was probably due to her serious general condition. In spite of the fact that a fluid wave was present, tympany also existed, and this, as well as the finding of air under the diaphragm, indicates the pressure of extraluminal gas. I am rather surprised that any peristalsis was heard. Certainly the lack of bowel function can be explained on the basis of widespread peritonitis; and I should like to explain the anuria on the basis of renal hypotension, secondary to the same process. In all probability, she had been in a state of relative shock forty-eight hours previous to hospital admission.

The few remarks about the past history are not helpful. The progressive fatigue could have been due to secondary anemia. " . . . many years previously she had had some sort of abdominal pain, which was in the midlower abdomen and spontaneously disappeared." This may have been due to any process — from appendicitis to dysmenorrhea. Perhaps I am dismissing this episode too lightly. We do know positively that the bowel habits had been regular and that she had had no urinary symptoms. This forces the conclusion that the present episode was acute and fulminating.

It is important that the initial discomfort was cramp-like and later became steady. This to me usually indicates that the organ involved was capable of peristalsis against an obstruction and that eventually there was perforation or disintegration, with local spread of the process. A tubular or a solid structure, such as an ovary, may twist on its pedicle repeatedly and finally infarct, but it is unlikely that such a process could persist over a matter of three weeks. We can also say that the organ under question probably contained gas or gas-producing micro-organisms. It is unlikely that blood-borne, gas-producing organisms, nurtured in an infarcted solid organ, would give such a picture at the end of five days.

One other point of note is the position of the pain—always in the lower abdomen. The initial sympathetic reference was into the lower abdomen, as well as the later somatic pain. The large bowel or genitourinary organs become the likeliest source of her disease.

From the x-ray films I should like to know the status of gas in the bowel and just where in the liver the air existed.

Dr. Stanley M. Wyman: This upright film of the chest shows the free air beneath the right half of the diaphragm, which is higher than usual. There appears to be some linear atelectasis in the base of the left lung field. The heart is not remarkable. The aorta is markedly tortuous; the proximal descending portion swings far to the right, and there is calcification in the wall.

This view, with the patient lying on her side, shows the gas beneath the diaphragm to move freely over the lateral surface of the liver. I am unable to see definite evidence of the suggested gas in the substance of the liver, but the liver is not well shown on the film of the abdomen. The free gas is seen lying high and medially. There is probably fluid in the abdomen, but no evidence of dilated loops of bowel. There is a lot of opaque material scattered throughout the abdomen, much of which may lie in the bowel. There is no mention of a previous barium examination or of the patient's taking medication. This appearance raises the question of calcification in an ovarian tumor, such as a papillary cystadenocarcinoma, although the shadows are unusually dense. This question cannot be answered unless we can exclude the possibility that the opaque material was in the bowel. I can see no evidence of unusual masses.

Dr. Donaldson: Air in the liver deserves special comment. It can get there by two routes. The usual course is via the biliary tree, in a retrograde fashion. Less frequently the portal blood stream conveys gas-producing bacteria, which are nurtured in the liver.

What could this have been? I am going to rule out the ureters and bladder. The uterus was small. This does not exclude it from torsion, infarction or perforation of a pyometrium. The age and marital status are compatible with spontaneous rupture of a pyometrium, but the organisms found are usually of many types and the pus is foul-smelling rather than odorless.

Torsion of a salpinx or ovarian cyst with late rupture should always be considered in an elderly patient, but it seems unlikely that free gas would be present within the abdomen and that the peritoneal fluid would show on smear gram-negative bacilli and cocci.

Could she have had a pancreatitis with ascites to throw her into such a state of collapse? I should have expected the collapse to have occurred days previously.

Appendicitis in elderly people rarely causes a textbook history, and epigastric symptoms are often lacking, particularly if there have been previous attacks. Inflammation of a Meckel's diverticulum, with perforation, seems unlikely since the pain was always in the lower abdomen.

Could this patient have passed a gallstone three weeks previously, which was wafted down the small bowel with mild symptoms and eventually became lodged in the large bowel? She gives no history of biliary dysfunction, and usually these stones become stuck in the region of a Meckel's diverticulum or at the ileocecal valve. If they do not cause obstruction and perforation in the small bowel, they should

pass through the large intestine. On the other hand, a spontaneous cholecystojejunostomy fistula is the most usual route of entry of gas within the liver shadow.

Against the diagnosis of diverticulitis of the large intestine with perforation is the lack of previous history of bowel difficulties, particularly constipation. Usually there is a long story of poor bowel habits, and in 18 per cent of Dr. Smithwick's* series there was a story of bleeding by rectum. The patient could have had leakage through a diverticulum with local abscess formation three weeks previously; and then, five days before admission, a fresh burst from the abscess, with the fatal result that so often follows a second peritoneal insult.

This patient probably had a tumor of the descending colon that had caused mild obstructive symptoms for three weeks and had finally ruptured. In disagreement with this diagnosis is the fact that there was no really dilated bowel by x-ray study. Three weeks of subacute intestinal obstruction should result in some degree of bowel dilatation, particularly in the presence of terminal peritonitis. Also, the pus obtained at tap was odorless. This bothers me considerably, although it is possible to obtain odorless pus from some cases of large-bowel perforation, such as when the appendix is involved. Certainly, perforation of such a tumor would result in free air within the peritoneal cavity, and by a pylephlebitis, gas-producing organisms might have been carried to the liver.

Clinical Diagnosis

Generalized peritonitis (cause unknown).

Dr. Donaldson's Diagnosis

Peritonitis, probably secondary to carcinoma of colon.

Anatomical Diagnoses

Benign peptic ulcer of stomach, with perforation and mesenteric abscess.

Perforation of mesenteric abscess, with generalized peritonitis.

Congenital anomalies: right-sided aorta and anomalous origin of left subclavian artery.

Arteriosclerosis.

Leiomyomas of uterus.

Carcinoids of ileum.

Pathological Discussion

Dr. Tracy B. Mallory: Dr. Donaldson was quite correct in predicting that the peritonitis in this case was due to a perforated viscus. He was also right in suggesting that the leakage occurred in two stages — first, local abscess formation and, later, rupture of the abscess with generalization of the peritonitis. He was completely wrong, however, in his localization of the process. Despite the fact that all the symptoms were lower abdominal, the primary lesion was in the stomach. We found a benign peptic ulcer high up on the posterior wall, only 7 cm. from the cardia, and close to the greater curvature. An abscess 7 cm. in diameter was present in the gastrocolic ligament that had a thick fibrous wall and was evidently of some weeks' duration. The abscess communicated through two small perforations with the lumen of the stomach through the base of the ulcer and with the general peritoneal cavity.

There were numerous incidental findings. The major arterial trunks were anomalous. The right common carotid and subclavian arteries arose separately from the aortic arch; the left subclavian artery was low and came off at the junction of the arch and descending aorta. The arch itself turned directly backward instead of crossing the vertebral column, and the descending aorta lay to the right of the trachea and of the vertebral column. Evidently there had been no cardiac embarrassment from this dextroposition, since the heart was of normal size.

The uterus contained several small fibroids and the ileum several carcinoid tumors, none of them large enough to have caused intestinal obstruction.

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EXUDATIVE TONSILLITIS AND PHARYNGITIS OF UNKNOWN ETIOLOGY

THE Commission on Acute Respiratory Diseases is again calling attention to a group of acute upper-respiratory-tract infections of unknown origin that it is important to differentiate from streptococcal infections of the throat.* In the course of studies on acute respiratory diseases carried out over a three-year period at Fort Bragg these workers encountered many cases of exudative tonsillitis and pharyngitis in which beta-hemolytic streptococci could not be incriminated as the causative agent. Indeed, it was quite conclusively demonstrated that about half the cases of tonsillitis and pharyngitis that they studied had neither bacteriologic nor serologic evidence of streptococcal infection.

*Commission on Acute Respiratory Diseases. Exudative tonsillitis and pharyngitis of unknown cause. *J. A. M. A.* 133:588-593, 1947.

Clinically, a comparison of the cases of unknown cause with those that were proved to be of streptococcal origin revealed distinctive characteristics of these groups as a whole, but the clinical findings were of little help in the differential diagnosis of individual cases. In general, the streptococcal infections had a more acute onset than the cases of unknown etiology. In the latter, chilliness, feverishness, headache and malaise — symptoms indicating systemic reaction — were slightly less frequent. On the other hand, the nonstreptococcal infections tended to involve the lower respiratory tract, as evidenced by the greater incidence of hoarseness, productive cough and pain in the chest. Sore throat and dysphagia were encountered with about equal frequency in both types of cases.

Physical examination also revealed some features that were helpful in the differential diagnosis. The patients in the streptococcal group gave the appearance of a more serious illness; they often showed diffuse redness of the mucous membranes of the palate, tonsils and posterior pharyngeal wall, and in the majority of them some edema of these tissues was also evident. Enlarged and tender lymph nodes, in particular, were more frequent in the cases of streptococcal infection. When caused by the streptococcus the tonsillar or pharyngeal exudate was usually yellow and extensive. By contrast the exudate seen in the nonstreptococcal cases was white or gray, was often of pinhead size and was frequently distributed over enlarged follicles of lymphoid tissue on the posterior pharyngeal wall.

The white-cell counts were also of some value in the differential diagnosis. Leukocytosis was a feature chiefly of the streptococcal cases, in which the average total count was about 13,000 with 79 per cent neutrophils, as compared with an average of about 9,000, with 67 per cent neutrophils, in the nonstreptococcal cases. Although both diseases are of short duration, with fever generally lasting less than four days, the maximum temperature tended to be higher in the streptococcal cases than in those of unknown cause; the average was 102.5 in the former, and 101.7°F. in the latter.

Although the differential diagnosis between the streptococcal and nonstreptococcal cases can ordinarily be made on clinical grounds, on the basis of

the criteria mentioned, cultures or serologic methods must be employed for accurate diagnosis. It is particularly important to differentiate these forms because the nonstreptococcal infection is a benign disease without important complications, whereas the streptococcal infections may give rise to serious and crippling sequelae. Intelligent management of such cases, therefore, requires cultural and serologic confirmation of the diagnosis.

The finding of streptococci in throat cultures may not always be adequate to establish a diagnosis, since normal subjects and those with undifferentiated respiratory infections may harbor streptococci, without the production of antibodies. Throat cultures from such persons, however, usually reveal only small numbers of streptococci, whereas the cultures in the true streptococcal infections, in which an antibody response is elicited, frequently yield a predominant growth of hemolytic streptococci.

The cause of the type of exudative tonsillitis and pharyngitis that the Commission on Acute Respiratory Diseases described is unknown. No single bacterial agent could be incriminated, and it was presumed to be a disease of nonbacterial origin. On epidemiologic grounds, it was thought that these cases might represent a variant of "epidemic undifferentiated acute respiratory disease." The incidence of this form of infection in civilian practice is not known, but it has been encountered with varying frequency, particularly in areas where epidemics of streptococcal infections have not been frequent or extensive. The suggestion is advanced that, because of the generally mild character of the disease, its short duration and the freedom from complications, this condition should be sought for among patients treated at home rather than among those treated in hospitals.

NONTUBERCULOUS PULMONARY CALCIFICATION

The methods generally used in surveys designed to discover cases of tuberculosis in its early stages and those intended to determine the probable incidence of the disease in the community include roentgenograms of the chest and tuberculin tests. The occurrence of demonstrable lesions in x-ray films, particularly areas of calcification with enlarged hilar nodes, has traditionally been considered to be evidence of tuberculous infection, and such lesions are usually accompanied by positive cutaneous reactions to tuberculin.

Recent surveys, particularly those in certain sections, such as Kansas City, Missouri, and Tennessee, have revealed a large number of persons with areas of calcification in their lungs and negative tuberculin tests.[1–5] Such a situation is ordinarily interpreted as evidence of anergy and is encountered in cases of miliary tuberculosis and sometimes during other active acute infections, notably measles. It is known, however, that certain other conditions, such as coccidioidomycosis in the active or end stage, may give similar roentgenographic findings, but the latter disease could not account for the findings in the recent studies.

Extensive studies in several areas among school children and student nurses have indicated a close correlation between the incidence of those who are tuberculin negative and x-ray positive and that of positive reactors to histoplasmin.[1–7] This is particularly close in persons with disseminated areas of calcification in the lungs. The findings suggest that histoplasmosis or some other disease that produces pulmonary lesions and results in sensitivity to histoplasmin is prevalent. Interestingly enough, the regions where the incidence of x-ray-positive, tuberculin-negative and histoplasmin-positive cases is the highest correspond to those from which proved cases of histoplasmosis have been reported. Among student nurses the area of highest incidence was found in the eastern central states, and the frequency of the occurrence of such cases diminished progressively in proportion to the distance from this area.[6]

The surveys that included histoplasmin skin tests have also resulted in the discovery of cases of active pulmonary disease among children in Kansas City, Missouri, and among student nurses in several states.[5] The pulmonary lesions simulated those of tuberculosis and eventually went on to calcification. There are no known criteria for differentiating these roentgenographic lesions and those of tuberculosis.

A review of the reported cases of histoplasmosis suggests that this is a highly fatal disease.[8] If the finding of positive reactors to histoplasmin is inter-

preted as evidence of infection with *Histoplasmosis capsulatum* or with some related organism, such a disease must be considered as existing chiefly in a benign and unrecognized form. Most workers who have been intimately concerned with these studies, however, are cautious in the interpretation of their findings,[8] partly because of the reports of cases of known and active histoplasmosis in which the skin tests with histoplasmin were negative[9, 10] and particularly because of the demonstration of marked cross reactions with histoplasmin in animals with experimental mycotic infections, including blastomycosis, coccidioidomycosis and moniliasis.[9, 11] The negative histoplasmin tests during active infection may be interpreted as evidence of anergy and are probably analogous to negative tuberculin tests in cases of miliary or other active forms of tuberculosis; they have been observed in severe disseminated and fatal cases of histoplasmosis.[9, 10]

Histoplasmosis is not known to occur in New England, but it has been reported from areas as close as New York and Washington, D. C. Unexplained pulmonary lesions, including disseminated areas of calcification, are encountered, however, that are not unlike those that have been described in Kansas City, Missouri, and Tennessee, which in those areas are associated with negative tuberculin reactions and positive cutaneous histoplasmin reactions. The possibility that some of these lesions in tuberculin-negative persons are the results of mycotic infections should be considered, particularly when other causes of disseminated pulmonary lesions can be excluded.

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MASSACHUSETTS MEDICAL SOCIETY

MEDICAL CARE FOR OLD-AGE ASSISTANCE

The following communication regarding rules relating to authorization and control of medical care for old-age assistance has been sent to all physicians in Boston by the Bureau of Old Age Assistance. It appears to be of sufficient importance to merit reprinting in the *Journal*.

Payment for doctor's service will be approved at a rate not to exceed $3.00 for a home visit and $2.00 for an office visit unless unusual circumstances warrant a higher payment.

Doctors are requested to notify the department immediately, to answer and return the medical inquiry promptly and to send bill to the recipient within fifteen days. Otherwise there may be a delay in payment.

Bills for excessive amounts and for an excessive number of visits and tardy bills are subject to review by the Medical Advisory Committee.

A rate not to exceed $5.00 a day for hospital care will be approved subject to the department's agreements with the hospitals. This rate includes all care, including service of a physician. It is expected that recipients in need of hospital care will obtain care in the large incorporated hospitals where adequate and economical service can be obtained.

Each recipient of old age assistance proved eligible for this medical assistance will be given an additional grant in accordance with the need. The recipient is directly responsible to the doctor and the hospital for payment of the obligation incurred.

JOSEPH GARLAND, *Secretary*

DEATHS

DAVIS — Max Davis, M.D., of Brookline, died April 30. He was in his forty-seventh year.

Dr. Davis received his degree from Harvard Medical School in 1925. He was assistant professor of obstetrics and gynecology, Boston University School of Medicine, and senior visiting physician, Gynecological Staff, Beth Israel Hospital, and was a diplomate of the American Board of Obstetrics and Gynecology, as well as fellow of The American College of Surgeons.

His widow survives.

DUTTON — Frank K. Dutton, M.D., of Springfield, died June 28. He was in his fifty-sixth year.

Dr. Dutton received his degree from Tufts College Medical School in 1915. He was a fellow of the American College of Surgeons and the American Medical Association.

His widow survives.

GORHAM — George H. Gorham, M.D., of Boston, died on March 12. He was in his seventy-seventh year.

Dr. Gorham received his degree from Tufts College Medical School in 1903.

CORRESPONDENCE

SALT-FREE BREAD

To the Editor: In view of the known importance of low-salt diets in the treatment of cardiac failure and also of hypertension, it appears to be important to call the attention of physicians in the vicinity of Boston to the fact that salt-free bread is now available through Betty Bakerite, Incorporated, at one of their local stores (235 North Beacon Street, Brighton). The manager informs me that if the demand for this bread becomes great enough it will be supplied through their various stores throughout the city.

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THERAPEUTIC ABORTION FOLLOWING RUBELLA

To the Editor: The progress article on rubella in the June 19 and 26 issues of the *Journal* was extremely interesting. The scientific approach to the etiology, course, differential diagnosis, complications, treatment and prevention was admirable.

The last three pages of the article, however, might just as well have been deleted from a scientific journal of medicine. The discussion of therapeutic abortion in cases of rubella in early pregnancy was highly philosophical and thus controversial and definitely not scientific. In addition, anyone with the slightest training in logic can discern numerous violations of ordinary common sense in this portion of the article.

Regardless of one's position in this disputed matter, I repeat that discussions of this type do not belong in a scientific medical journal. If one has opinions or strong feelings on morality, euthanasia, the Bible or witches, such opinions, it seems to me, should not be included in medical articles.

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Dr. Paganini's letter was referred to Dr. Conrad Wesselhoeft, the author of the article in question. His reply is as follows.

To the Editor: The criticism of the discussion of abortion in the progress review on rubella brings to mind a letter on the subject in the *British Medical Journal* (Barry, W. K. Correspondence: Rubella and pregnancy. *Brit. M. J.* 1: 423, 1947) that goes far beyond discerning "numerous violations of ordinary common sense." This English physician refers to abortion as murder and insists that as such this operation is never justifiable and, in the case of rubella in early pregnancy, is a "massacre of the innocents."

The advancement of medical knowledge exerts a profound influence on public opinion and on the enactment of laws pertaining to human welfare. The mission of the medical profession is concerned not alone with scientific research and administering to the sick but also with preventive medicine. The carrying out of any preventive measures is dependent on enlightened public opinion and frequently involves overcoming deep-rooted beliefs. Vaccination against smallpox is a typical example.

In the discussion of the application of newer knowledge of rubella in early pregnancy, it seemed appropriate to bring out the historical background. The ancient concept that congenital defects resulted from witchcraft led me quite naturally to the original biblical commandment and to the evolution of laws pertaining to it. This approach assailed an ancient tenet that has been rendered obsolete through public opinion and the enactment of radical changes in the law.

The statutes relative to abortion have been amended to conform to our newer knowledge of disease without endangering the intent of the original law. After presenting the possibilities of congenital deformities following rubella in early pregnancy and the resulting unfortunate determent to future pregnancies, I emphasized the purpose of the existing law and finished with an appeal for the consideration of a further amendment to cover this particular situation for the betterment of suffering humanity. The fundamental purpose of religion, medicine and the law is to help mankind. When this purpose fails, it is the fault of the frailties of human nature, and correction is due.

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BOOK REVIEWS

Agnosia, Apraxia, Aphasia: Their value in cerebral localization. By J. M. Nielsen, M.D. Second edition, completely revised. 8°, cloth, 292 pp., with 59 illustrations. New York: Paul B. Hoeber, Incorporated, 1946. $5.00.

The elucidation of the many problems associated with speech defects has long been of interest to the medical profession. From the time of Broca through the work of Head in England and Starr and Mills in America, there has been a continued interest in this problem. In recent years the outstanding investigator has been the author of this monograph. The first edition was published privately in 1936, when the enthusiasm for the study of aphasia and allied conditions was not great. The matter, however, was kept open by the continued investigations of Dr. Nielsen, and his first publication did not fall on sterile ground. Indeed, it was welcomed in many places where research was going forward. Now, ten years later he has expanded the book into a second edition of increased usefulness.

In various chapters he covers a brief history of the knowledge of aphasia, apraxia and agnosia. He then outlines the theories regarding causation of these conditions and details each in a separate section of the book. After giving the methods of examination used clinically in the elucidation of the signs of speech defects, he presents the bulk of his monograph in a careful analysis of the pathologic material observed by him over a period of many years and carefully correlated with the clinical evidence in each case. The volume closes with an appendix on nomenclature and a selected bibliography.

The book will be of use to the clinical neurologist who has to meet the acute problem of aphasia, to the neurologic surgeon who needs to know the aphasic syndromes as an aid to localization and to the growing numbers of investigators who are attempting to untangle one of the most complicated of all problems in neurology. There is still much to learn, but no better basis for advancing knowledge can be found than the text provided by Dr. Nielsen in the present edition of an outstanding monograph.

Carbohydrate Metabolism: Correlation of physiological, biochemical and clinical aspects. By Samuel Soskin, M.D., and Rachmiel Levine, M.D. 8°, cloth, 315 pp., with 42 tables. Chicago: University of Chicago Press, 1946. $6.00.

The authors state in the preface that "the volume is intended to serve as a correlative text for the teaching of carbohydrate metabolism to students of physiology, biochemistry and medicine." The average medical practitioner who consults the book may find a large part of it bewildering. He may feel beyond his depth as he reads the early chapters dealing with the "enzymatic machinery" and other matters concerned with intermediary metabolism. Also, he will probably find many of the ideas that he has cherished regarding metabolism flatly contradicted.

The following quotation illustrates the iconoclastic attitude and diction of the authors:

> It is clear that neither the low R.Q. of diabetes nor the failure of the R. Q. to rise following the administration of sugar constitutes evidence for a lack of ability to oxidize carbohydrate . . . one must conclude that chemical balance studies offer neither theoretical nor actual support for the R.Q. as a measure of dissimilation. Since no other validation of the R.Q. is available at the present time, one must go further and say that there is no evidence that the R.Q. is a measure of dissimilation.

Concerning the dextrose-nitrogen ratio they write, "We may summarize the present knowledge by saying that whatever its empirical usefulness the figure of 44–58 per cent commonly used in metabolic and nutritional work to calculate the carbohydrate equivalent of protein has no real basis of fact." In reference to ketosis they state:

> It is thus no longer proper to speak of anti-ketogenesis in the sense so long employed by clinicians by which they actually meant ketolysis (ketone oxidation). In view of present knowledge, the various ketogenic, anti-ketogenic ratios which have been used to calculate the amounts of carbohydrates necessary for oxidation of the ketone bodies must be regarded as being without any real significance.

Soskin has been a strong proponent of the theory that the fundamental metabolic defect in diabetes is overproduction of sugar, contrary to the theory popularly held in the past that there is loss of the capacity to utilize sugar. The work that he and his collaborators have done to support this view and to develop new ideas regarding carbohydrate metabolism is discussed in detail. In presenting controversial points, Soskin has tried to be impartial, but his critics may claim that he has not always succeeded.

The direct clinical applications of the book are limited. Indeed, such clinical recommendations as the use of the intravenous glucose-tolerance test as a criterion of liver function and the opinion of the authors concerning the alleged need for large amounts of sugar or other carbohydrates in the treatment of diabetic coma are not likely to receive general acceptance.

Progress in medical practice cannot be made unless there is readiness to relinquish unsound concepts. Soskin and Levine will give a healthy stimulus to those whose ideas are fixed by prejudice or misinformation.

The American Hospital. By E. H. L. Corwin, Ph.D. Studies of the Committee on Medicine and the Changing Order, New York Academy of Medicine. 8°, cloth, 226 pp. New York: The Commonwealth Fund, 1946. $1.50.

In this special monograph Dr. Corwin presents a factual analysis of existing hospital conditions in the United States. He points out that although the present hospital plant represents an investment of five and a half billion dollars it has reached this magnitude through unorganized effort and not by conscious planning.

The first chapter reviews briefly the history of hospital information from the time of the first list, compiled by Dr. J. M. Toner in 1873, to the present. The second discusses the hospital domain, embracing the development, types and ownership of hospitals. It is well documented with charts and tables. The statistics for 1943 show a total of 6655 hospital institutions of all kinds in the country, with a total bed capacity of 1,649,254 — or about 1 hospital bed for every 80 persons in the gross population. One of every 10 persons in the United States is admitted annually to a hospital. The third chapter deals with hospital finance and analyzes plant assets, investment sources, including the increasing governmental participation, operating costs and income from various sources. The succeeding chapters discuss the distribution and utilization of hospital facilities, the hospital as employer and as a training ground, personnel and administration, medical service and the outpatient department and the housing of hospitals.

The uneven distribution of hospital facilities is analyzed, and the effect of urbanization and industrial centralization is emphasized. Efforts to increase and improve hospital facilities, including prepayment plans, Blue Cross, workmen's compensation, inclusive-rate and moderate-rate plans, are gone into in detail. Medical service is discussed from the viewpoints of organization and standardization.

In the final chapter, under the heading "Retrospect and Prospect," an attempt is made to summarize the significant facts brought out in the previous chapters and to examine the future of the hospital. The topics discussed include the importance of the general hospital, dependence of local governments on voluntary hospitals, nonprofit basis of hospital investment, size of hospitals, rising costs and cost accounting, sources of revenue, utilization of hospitals, domiciliary care of sick patients, chronic and convalescent, estimate of postwar needs, research, public-health and preventive medicine and pathometry, or the use of hospital statistics.

A list of selected references is appended to each chapter, and a good index concludes a well published volume. It contains a mass of authoritative data, and is recommended for all medical libraries as well as public libraries and hospital administrators.

The Second Forty Years. By Edward J. Stieglitz, M.D. With a foreword by Anton J. Carlson, Ph.D., LL.D., M.D., Sc.D. 8°, cloth, 317 pp., with 18 figures. Philadelphia: J. B. Lippincott Company, 1946. $2.95.

In this semipopular book Dr. Stieglitz presents a guide to longer life and considers the problems incident to the aging of the person over forty. The biology and hazards of senescence are comprehensively discussed. It is interesting to note that the average life span has increased from twenty-one years at the time of the Holy Roman Empire to sixty-six years in 1944.

The rate of aging is rapid from birth to forty years, and slow from forty to a hundred years, on a chart it is almost a straight drop to twenty years, and about a flat line from fifty years on. Statistical graphs point out an interesting situation: in 1900, persons of sixty-five years and over comprised 4.1 per cent of the population; in 1940, the figure had increased to 6.8 per cent; and it is estimated that in 1980 the percentage will have increased to 14.4. The percentages of persons under five years of age during the same periods are, respectively, 12.1, 8 and 6.4. The life expectancy from birth was forty years in 1850, forty-seven years in 1900 and sixty-three years in 1940, and if the increase continues in that proportion to 1980 the span may reach seventy to seventy-five years. These statistics reveal a decline in the birth rate and an increase in the life span, a serious problem.

There are special chapters on heart disease, high blood pressure, cancer, nutrition, sex and age, mental changes and the wise use of leisure. The final chapter discusses the relation of an aging people to society.

The book contains practical advice for the elderly on how to eat, play, think and face the threats of chronic disease. It is an unusual, outstanding treatise by a competent medical authority and should be in all libraries, medical and public. The volume is well published in every way.

The Chest: A handbook of roentgen diagnosis. By Leo G. Rigler, M.D. 8°, cloth, 352 pp., with 338 illustrations. Chicago: Year Book Publishers, Incorporated, 1946. $6.50.

The greatest limitation in the atlas type of presentation of radiologic texts has been the poor quality of reproductions. In this volume the problem is well handled in handbook form. The illustrations are numerous and of good quality, and are captioned by descriptions and interpretations of specific examples of roentgenologic changes in diseases of the lungs, bronchi, mediastinum and pleura. Primary heart changes and lesions of the thoracic cage have been omitted, since they are outside the scope of the book. The pathological and physiologic aspects of diseases of the chest are discussed only so far as they are relevant in roentgenologically evident lung changes.

The presentation is sound, and the descriptions are lucid; the organization for reference, however, is poor, and the book is not inclusive enough for a reference on chest diseases.

In the field of chest diagnosis, in which the roentgenologic interpretation stands unrivalled as the most rewarding single procedure, the internist should find this book an elucidating text and a helpful guide. The student of roentgenology will also find it excellent for preliminary orientation.

Mongolism and Cretinism: A study of the clinical manifestations and the general pathology of pituitary and thyroid deficiency. By Clemens E. Benda, M.D. 8°, cloth, 310 pp., with 101 illustrations and 48 tables. New York: Grune and Stratton, 1946. $6.50.

This monograph is based on the study of a large series of cases of mongolism and cretinism seen at a state school for mental deficiency. The study covers all aspects of both diseases in an adequate, scholarly manner and thus brings to the attention of physicians a complete review of present knowledge of the two distressing conditions. Most of the book deals with mongolism, and the conclusions are based on the observations of more than 300 patients. Dr. Benda adds greatly to knowledge of the hereditary aspects of the problem, as well as its relation to the pregnancy of the mother and the order of birth. He believes that mongolism is due to deficiency of the anterior portion of the pituitary gland — a point that is not conceded by many investigators. Factors other than endocrine are needed to explain all the aspects of mongolism. Moreover, treatment by glandular preparations has not been satisfactory, even in Dr. Benda's hands.

The format of the book, the illustrations and the bibliography are beyond criticism. The monograph will be of particular interest to pediatricians and obstetricians.

Introduction to Surgery. By Virginia K. Frantz, M.D., and Harold D. Harvey, M.D. 12°, cloth, 216 pp. New York: Oxford University Press, 1946. $2.50.

This is a pocket-sized volume with an excellent index and extensive up-to-date references. Well adapted for the beginner, it is concise and clear and presents the elements of surgery in a simple, readable manner. It is especially recommended for medical students.

(*Notices on page xiii*)